

## 16.1.1 PROTOCOL

### Protocol and Protocol Amendments

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Final Protocol	4.1	11 September 2015
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Notes-to-File	NA	09 March 2016

NA=not applicable.



## Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

EudraCT No: 2014-002011-41

Sponsor: TESARO, Inc.

1000 Winter Street, Suite 3300  
Waltham, MA 02451 USA

TESARO Medical Monitor:

PI [REDACTED] MD, MPH  
Senior Medical Director

Principal Investigator:

PI [REDACTED], MD, PhD  
PI [REDACTED]  
PI [REDACTED], NL

Contract Research Organization:

PPD  
929 North Front Street  
Wilmington, NC 28401 USA

Version of Protocol: 4.1

Original Final Protocol Date: 28 May 2014

Amendment 1: 04 December 2014

Amendment 2: 17 March 2015

Amendment 3: 11 September 2015

This clinical investigation will be conducted according to this clinical protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki (Version 2008), and with other applicable regulatory requirements.

### Confidentiality Statement

All information contained in this document is privileged and confidential to TESARO. Any distribution, copying, or disclosure is strictly prohibited without prior written approval by TESARO.

## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

### Declaration of the Principal Investigator

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Principal Investigator	PI
Name:	PI
Title:	PI
Institution:	PI
Date: 01/12/2015	

## SPONSOR SIGNATURE PAGE

### Declaration of Sponsor or Responsible Medical Expert

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

#### Sponsor Signatory

PI  
PI MD, PI PH  
Senior Medical Director  
TESARO, Inc.

16 Sept 2015

Date

## SYNOPSIS

<b>Name of Sponsor/Company:</b> TESARO, Inc.	
<b>Name of Investigational Product:</b> Niraparib	
<b>Name of Active Ingredient:</b> Niraparib	
<b>Title of Study:</b> Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer (Protocol Number PR-30-5015-C)	
<b>Study Center(s):</b> A single study center in the Netherlands	
<b>Principal Investigator:</b> PI [REDACTED], MD, PhD <b>Investigators:</b> Not applicable	
<b>Studied Period (years):</b> Estimated date first subject enrolled: February 2015 Estimated date last subject completed: December 2015	<b>Phase of Development:</b> 1
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"><li>To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer</li></ul> <b>Secondary:</b> <ul style="list-style-type: none"><li>To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer</li><li>To evaluate the safety and tolerability of niraparib in subjects with cancer.</li></ul>	
<b>Methodology:</b> This is an open-label study with 2 parts, plus an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP). <b>Part 1:</b> The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration on Day 1. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling. <b>Part 2:</b> The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study	

center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity ( $3 \times 100\text{-mg capsules, labeled active pharmaceutical ingredient } [3 \times 33.3 \mu\text{Ci of radioactivity}]$ ), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. Participation in Part 2 of the study may extend beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm 24$  hours of the final urine or fecal sample.

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [ $3 \times 100\text{-mg capsules, unlabeled active pharmaceutical ingredient}$ ] of niraparib) once a day (QD) and will undergo safety assessments. No fasting period is required during the extension study. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject ([Section 3.4](#)). Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

**Number of Subjects (planned):**

**Part 1:** 6 subjects

**Part 2:** 6 subjects

Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

**Diagnosis and Main Criteria for Inclusion:**

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has a histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy; or have progressed despite standard therapy; or

has refused standard therapy (or for which no standard therapy exists); and subject may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.

4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 150,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL}$  (5.6 mM)
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 4.3](#)).
8. Subject is able to take oral medications.
9. Subject must agree to blood samples during screening and at the end of treatment for cytogenetic analysis.

**Exclusion Criteria:**

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has any known, persistent ( $>4$  weeks)  $\geq\text{Grade } 3$  hematological toxicity or fatigue from prior cancer therapy.
4. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
5. Subject has known hypersensitivity to the components of niraparib.
6. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
7. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava

- syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
8. Subject received (or is anticipated to receive) a platelet transfusion within 4 weeks of study drug administration.
  9. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
  10. Subject has any known history of myelodysplastic syndrome (MDS) or a pre-treatment cytogenetic testing result at risk for a diagnosis of MDS/acute myeloid leukemia (AML).
  11. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
  12. Subject is immunocompromised with an active event and is being treated with medications.
  13. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
  14. Subject has a corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.
  15. Subject is receiving concomitant medications that prolong QTc and is unable to discontinue use for the duration of the study ([Appendix 16.1](#)).
  16. Subject is starting chemotherapy within 3 weeks of study drug administration.
  17. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
  18. Subject has a history of illicit drug use.
  19. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
  20. Subject is currently participating in another clinical study and has received an investigational drug, or has participated in a clinical study and has received an investigational drug within 21 days of study drug administration.
  21. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months prior to study drug administration (for subjects participating in Part 1) or within 30 days prior to study drug administration (for subjects participating in Part 2).

**Investigational Product, Dosage and Mode of Administration:**

**Part 1:** Niraparib 300 mg (3 × 100-mg capsules) orally and [<sup>14</sup>C]-niraparib 100 µg (1 µCi total radioactivity) intravenously

**Part 2:** [<sup>14</sup>C]-niraparib 300 mg (3 × 100-mg capsules; 3 × 33.3 µCi radioactivity [100 µCi total radioactivity]) orally

**Extension study:** Niraparib 300 mg (3 × 100-mg capsules) orally

**Duration of Treatment:**

**Part 1:** Administration of a single oral dose, followed by a 15-minute IV infusion 2 hours after administration of the single oral dose

<p><b>Part 2:</b> Administration of a single oral dose</p> <p><b>Extension Study:</b> QD administration until treatment discontinuation</p>
<p><b>Reference Therapy, Dosage and Mode of Administration:</b></p> <p>None.</p>
<p><b>Criteria for Evaluation:</b></p> <p><b>Pharmacokinetics:</b></p> <p><b>Part 1:</b> Plasma niraparib concentrations will be used to determine the following PK parameters: maximum observed plasma concentration (<math>C_{max}</math>); time to reach <math>C_{max}</math> (<math>T_{max}</math>); and area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration (<math>AUC_{0-last}</math>); and if the data allow: AUC from time 0 to infinity (<math>AUC_{0-inf}</math>); apparent oral volume of distribution (Vd/F); apparent oral clearance (CL/F); and half-life (<math>t_{1/2}</math>). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.</p> <p><b>Part 2:</b> Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters: <math>C_{max}</math>, <math>T_{max}</math>, and <math>AUC_{0-last}</math>. The plasma niraparib concentration will be used to determine the following PK parameters: <math>C_{max}</math>, <math>T_{max}</math>, and <math>AUC_{0-last}</math>, and if the data allow: <math>AUC_{0-inf}</math>, Vd/F, CL/F, and <math>t_{1/2}</math>. Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period, <math>A_e</math>(day), and total amount of drug excreted in the urine, <math>A_e</math>(total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption (f), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.</p> <p><b>Safety:</b></p> <p>Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.</p>
<p><b>Statistical Methods:</b></p> <p><b>Pharmacokinetics:</b></p> <p>For Part 1, plasma concentrations based on the radioactivity and mass spectrometry (MS) ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure. For Part 2, whole blood and plasma concentrations based on the radioactivity and MS ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.</p> <p><b>Safety:</b></p> <p>All AEs will be listed and tabulated. Physical examination findings, vital signs, ECG parameters, and clinical laboratory results will be listed and summarized using descriptive statistics.</p>

**Table 1: Schedule of Assessments: Part 1\***

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X												X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X <sup>c</sup>	X	X	X <sup>d</sup>	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>d</sup>	X												
Clinical laboratory assessment <sup>e</sup>	X <sup>f</sup>												X X
Serum pregnancy test (women of childbearing potential)	X												X
Electrocardiogram (12-lead) <sup>g</sup>	X		X										X
ECOG performance status	X												X <sup>h</sup>
Confirm diagnosis with CT scan <sup>i</sup>	X												
Subject confinement		X <sup>c</sup>	X	X	X	X							
Niraparib oral administration <sup>j</sup>			X										
[ <sup>14</sup> C]-niraparib IV infusion <sup>k</sup>			X										

**Table 1: Schedule of Assessments: Part 1\* (Continued)**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Pharmacokinetic blood sampling <sup>i</sup>			X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>m</sup>	X	X <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous

\*Note: No modifications have been made to Part 1 assessments for MDS/AML monitoring, as all Part 1 subjects had either exited the study or progressed to the Extension study by the date of Amendment 3 Protocol approval.

<sup>a</sup> Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration on Day 1.

<sup>b</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature ([Section 8.1.4](#)). On Day 1, vital signs should be collected prior to study drug administration.

<sup>c</sup> If subject comes to the center and/or chooses to be admitted on Day -1.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>f</sup> Must occur within 72 hours prior to dosing.

<sup>g</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>h</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see [Section 8](#)).

<sup>i</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>j</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>k</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>l</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [within 1 min prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 [within 1 min post-infusion], 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose),

Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>m</sup>New adverse events (AEs) and serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit, or until new anticancer therapy is initiated.

**Table 2: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																		
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup>	End of Part 2
Informed consent	X																		
Subject demographics and baseline characteristics	X																		
Medical history and cancer history	X																		
Inclusion/exclusion criteria	X																		
Physical examination	X																	X	
Height (cm)	X																		
Weight (kg)	X																	X	
Body mass index (kg/m <sup>2</sup> )	X																		
Vital signs <sup>c</sup>	X	X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HBV/HCV/HIV screening <sup>e</sup>	X																		
Clinical laboratory assessments <sup>f</sup>	X <sup>g</sup>																X	X	
Serum pregnancy test (women of childbearing potential)	X																	X <sup>h</sup>	
Electrocardiogram (12-lead) <sup>i</sup>	X		X															X	
ECOG performance status	X																	X <sup>h</sup>	
Confirm diagnosis with CT scan <sup>j</sup>	X																		
Subject confinement		X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
[ <sup>14</sup> C]-niraparib oral administration <sup>k</sup>			X																

**Table 2: Schedule of Assessments: Part 2 (Continued)**

Assessment or Procedure	Day Relative to First Dose of Study Drug																		
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup>	End of Part 2
Pharmacokinetic blood sampling <sup>l</sup>		X	X	X	X	X	X			X			X					X	X <sup>l</sup>
Blood sample for metabolite profiling <sup>m</sup>		X	X	X	X	X	X			X			X					X	X
Urine collection <sup>n</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Fecal collection <sup>o</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Bone marrow aspirate and biopsy sample collection (whole blood) for cytogenetic analysis <sup>p</sup>																			X
Whole blood samples for cytogenetic analysis <sup>q</sup>	X																		X <sup>r</sup>
Whole blood sample for FISH, MDS	X <sup>s</sup>																		
Prior/concomitant medication and AE monitoring <sup>t</sup>	X	X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X			X	X	

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration on Day 1.

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote <sup>n</sup> and Footnote <sup>o</sup>), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped. Note that only urine/fecal and PK blood collections may extend beyond Day 22; other assessments do not need to be repeated.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature ([Section 8.1.4](#)). On Day 1, vital signs should be collected prior to study drug administration.

<sup>d</sup> If subject comes to the center and/or chooses to be admitted on Day -1.

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>f</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>g</sup> Must occur within 72 hours prior to dosing.

<sup>h</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see [Section 8](#)).

<sup>i</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>j</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>k</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity (3 × 100-mg capsules, labeled active pharmaceutical ingredient [3 x 33.3 µCi of radioactivity]), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<sup>l</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose). Participation in Part 2 of the study may extend beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm$  24 hours of the final urine or fecal sample ([Section 7](#)).

<sup>m</sup> Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>n</sup> Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. See [Section 7.2](#) for collection stop criteria.

<sup>o</sup> Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. See [Section 7.3](#) for collection stop criteria.

<sup>p</sup> For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the local hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria (Vardiman 2009) and other sample testing results related to MDS/AML. Report data will be entered into EDC on the appropriate eCRE pages and the site must keep a copy of all reports with the subject's study file.

<sup>q</sup> Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Laboratory Manual.

<sup>r</sup> Blood sample for cytogenetic analysis only if subject discontinues.

<sup>s</sup> FISH, MDS test result must be negative for cytogenetic abnormalities commonly observed in myeloid malignancies. The FISH, MDS result must be received prior to randomization.

<sup>t</sup> New adverse events (AEs) and serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit, or until new anticancer therapy is initiated.

**Table 3: Schedule of Assessments: Open-Label Extension Study**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c, d</sup>
		Day 1	Day 8	Day 15	Day 22		
Inclusion/exclusion criteria	X						
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>e</sup>	X	X	X	X	X	X	X
Complete blood count (CBC) <sup>f</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>g</sup>	X			X		X	X
Pregnancy test (women of childbearing potential) <sup>h</sup>	X					X	X
Study drug dispensed/collected <sup>i</sup>		X				X	X
Electrocardiogram (12-lead) <sup>j</sup>		X				X	X
ECOG performance status	X					X	X
Niraparib oral administration (in-house) <sup>k</sup>		X	X	X	X	X	
Bone marrow aspirate and biopsy sample collection (whole blood) for cytogenetic analysis <sup>l</sup>					X		
Whole blood samples for cytogenetic analysis <sup>m</sup>	X						X
Whole blood samples for FISH, MDS	X <sup>n</sup>						

**Table 3: Schedule of Assessments: Open-Label Extension Study (Continued)**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c, d</sup>
		Day 1	Day 8	Day 15	Day 22		
Concomitant medication and AE monitoring <sup>e</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

a Upon completion of Part 1 or 2 of the study (or if subject is non-evaluable for PK in Part 1 or 2), subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit.

b Treatment cycles are 28 ( $\pm 3$ ) days. Visits (except Cycle 1) will continue approximately every 4 weeks until treatment discontinuation

c The EOT visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)). If the subject discontinues due to disease progression, then the CT scan (taken per standard of care) closest to the time of progression (EOT) should be provided.

d New malignancy information will be collected for all subjects via telephone every 90 days following the treatment discontinuation visit (subjects in the extension study only). See [Section 8.1.12](#).

e Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature ([Section 8.1.4](#)). On Day 1, vital signs should be collected prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.

f The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.

g Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.

h A serum pregnancy test will be conducted at the Screening Visit and at EOT. A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4/Day 1, Cycle 7/Day 1, etc.).

i Subjects will take 300 mg (3  $\times$  100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. No fasting period is required during the extension study. No new capsules will be dispensed at EOT.

j Subjects will have a 12-lead ECG at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at EOT.

k Niraparib is self-administered daily, except on study visit days. On days of study visits (eg, Cycle 1, Day 1, 8, 15, and 22; Cycle n, Day 1) subjects should refrain from taking niraparib until after clinical assessments are performed.

<sup>1</sup> For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the local hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria (Vardiman 2009) and other sample testing results related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the subject's study file.

<sup>m</sup> Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Laboratory Manual.

<sup>n</sup> FISH, MDS test result must be negative for cytogenetic abnormalities commonly observed in myeloid malignancies. The FISH, MDS result must be received prior to randomization.

<sup>o</sup> New adverse events (AEs) and serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit, or until new anticancer therapy is initiated.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 4: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
ADP	adenosine diphosphate
AE	adverse event
A <sub>e</sub> (day)	amount of drug excreted in the urine in a 24-hour period
A <sub>e</sub> (total)	total amount of drug excreted in the urine
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AMS	accelerator mass spectrometry
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC <sub>0-inf</sub>	area under the plasma concentration-time curve from time 0 to infinity
AUC <sub>0-last</sub>	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
CA-125	cancer antigen 125
CBC	complete blood count
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent oral clearance
C <sub>max</sub>	maximum observed plasma concentration
CNS	central nervous system
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	cytochrome P450 1A2
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
f	extent of absorption

**Table 4: Abbreviations and Specialist Terms (Continued)**

Abbreviation or Specialist Term	Explanation
GCP	good clinical practice
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	homologous recombination
IB	investigator's brochure
IC <sub>20</sub>	20% maximum inhibitory concentration
IC <sub>50</sub>	50% maximum inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
LC-MS	liquid chromatography-mass spectrometry
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LSC	liquid scintillation counting
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
MS	mass spectrometry
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
P-gp	P-glycoprotein
PARP	poly (adenosine diphosphate-ribose) polymerase
PI	principal investigator
PK	pharmacokinetic
QD	once a day
QTc	corrected QT interval

**Table 4: Abbreviations and Specialist Terms (Continued)**

Abbreviation or Specialist Term	Explanation
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
$T_{max}$	time to reach maximum observed plasma concentration
ULN	upper limit of normal
Vd/F	apparent oral volume of distribution

## 1. INTRODUCTION

### 1.1. Niraparib

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally active poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor with nanomolar potency that is being developed for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway or that are driven by PARP-mediated transcription factors.

#### 1.1.1. DNA Repair, Cancer, and PARP Inhibition

The PARP-1 and -2 enzymes, which are zinc-finger DNA-binding enzymes, play a crucial role in DNA repair. Upon formation of single-strand DNA breaks, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones, various DNA repair proteins, and PARP itself, which results in chromatin relaxation and fast recruitment of DNA repair factors that access and repair DNA breaks.

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of tumor cells than on normal cells. Therefore, a hypothesis is that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways.

Clinical studies have shown that PARP inhibitors have antitumor activity in certain types of cancer (Fong et al, 2009; Audeh et al, 2010; Gelmon et al, 2011; Kummar et al, 2012; Ledermann et al, 2012). Nonclinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with homozygous inactivation of either *BRCA-1* or *BRCA-2*; these breast cancer genes are known to be important in the HR DNA repair pathway. Germline mutations of *BRCA-1* and -2 are found in the majority of subjects with inherited breast or ovarian cancer. Inactivation of *BRCA-1* and -2 by mechanisms other than mutations, including somatic mutations and gene silencing by promoter hypermethylation, occurs in a significant portion of several sporadic cancers. In particular, for ovarian cancer, somatic *BRCA-1* or -2 mutations are found in 10% to 15% of all epithelial ovarian carcinomas, and strongly reduced expression of *BRCA-1* has been observed in a significant portion of sporadic ovarian cancers. Collectively, up to 40% to 60% of ovarian cancers might be responsive to PARP inhibitors as a consequence of defects in the BRCA-HR pathway, indicating a great potential for this approach in the therapy of ovarian cancer.

#### 1.1.2. Niraparib Nonclinical Studies

Niraparib inhibits normal DNA repair mechanisms and induces synthetic lethality when administered to cells with HR defects. In a *BRCA-1* mutant xenograft study in mice, niraparib dosed orally caused tumor regression, which was mirrored by a greater than 90% reduction in

tumor volume compared to control. In a *BRCA-2* mutant xenograft study in mice, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib was evaluated for its potential effects on cardiovascular and neurological function using several experimental safety pharmacology models. Niraparib inhibited the human Ether-à-go-go-related gene (hERG) current with a 50% maximal inhibitory concentration ( $IC_{50}$ ) value of 10  $\mu$ M and a 20% maximal inhibitory concentration ( $IC_{20}$ ) value of 3.8  $\mu$ M. Niraparib was administered intravenously during 3 sequential 30-minute periods at 1, 3, and 10 mg/kg to determine the effect of niraparib on cardiovascular function in 3 anesthetized dogs. Niraparib had no effect on the corrected QT interval (QTc; average plasma concentration  $\leq$ 15.3  $\mu$ M at 10 mg/kg). Mean arterial pressure and heart rate were increased at all doses evaluated, but the QRS cardiac interval was only increased at 10 mg/kg. Niraparib had no effect on neurological function in conscious mice at a single oral dose of 100 mg/kg.

The pharmacokinetics (PK) of niraparib in male Sprague-Dawley rats were determined following intravenous (IV; 3 mg/kg) and oral (5 mg/kg) administration. In male beagle dogs, PK studies were conducted following IV (1 mg/kg) and oral (3 mg/kg) administration. Following IV administration, niraparib demonstrated moderate-to-high clearance (28 and 31 mL/min/kg), a high volume of distribution (6.9 and 12.3 L/kg), and moderate terminal half-lives (3 and 6 hours) in rats and dogs, respectively. The oral bioavailability of niraparib was reasonable in both species (approximately 27% in rats and 57% in dogs).

Niraparib was investigated in 1-month oral toxicity studies in order to support daily dosing of the compound in humans, where niraparib was administered to rats and dogs by oral gavage once a day (QD) for up to 4 weeks followed by an approximately 2-week recovery period. Overall, nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. In the 1-month repeat-dose toxicity study in rats, mortality and physical signs were limited to the high dose (50 mg/kg/day). All changes observed at 50 mg/kg/day were resolved at the end of the 2-week recovery period or demonstrated reversibility, except for minimal treatment-related arterial hypertrophy in the heart and increased trabecula in the bone. At 10 mg/kg/day, there were no treatment-related changes other than increased urine volume in males. Based on these findings, the no observed adverse effect level (NOAEL) in the rat study was 10 mg/kg/day. The dose causing severe irreversible toxicity and death was 50 mg/kg/day. In the dog, decreases in hematology values were observed at a dose of 15 mg/kg/day, and all hematology changes seen during the dosing phase were resolved at the end of the recovery period. Although a decrease in amount of spermatogenic epithelium was observed after 1-month dosing at 6 mg/kg/day and 15 mg/kg/day and was not resolved at the end of the 2-week recovery period, the continued presence of spermatogenic epithelium supports that this change would eventually resolve. Therefore, based on these findings, the NOAEL for the dog study was 3 mg/kg/day.

The niraparib nonclinical studies are described in detail in the [Investigator's Brochure \(IB\)](#).

### **1.1.3. Niraparib Clinical Studies**

The niraparib clinical studies are described in detail in the [IB](#).

### 1.1.3.1. Phase 1 Studies

Niraparib has been evaluated in a series of Phase 1 clinical studies in subjects with solid tumors. For these studies, niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide. Treatment with niraparib has been generally well-tolerated. Refer to the Investigator's Brochure for more information.

The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were fatigue, nausea, anemia, constipation, thrombocytopenia, vomiting, decreased appetite, neutropenia, headache, diarrhea, dyspnea, cough, leukopenia, hyponatremia, back pain, hyperglycemia, insomnia, abdominal pain, hypokalemia, blood alkaline phosphatase increased, pain in extremity, hypertension, peripheral edema, rash, dizziness, electrocardiogram (ECG) QT prolonged, pyrexia, abdominal distension, urinary tract infection, weight decreased, abdominal pain lower, alopecia, neoplasm malignant, dry mouth, hypoalbuminemia, musculoskeletal pain, stomatitis, arthralgia, blood creatinine increase, chills, dyspepsia, hypomagnesemia, paresthesia, aspartate aminotransferase increased, dehydration, musculoskeletal chest pain, neck pain, alanine aminotransferase (ALT) increased, dysgeusia, myalgia, and palpitations.

The most commonly reported drug-related (>5.0%) AEs (all grades) in the clinic were: fatigue, nausea, anemia, thrombocytopenia, decreased appetite, neutropenia, vomiting, constipation, leukopenia, diarrhea, insomnia, dyspnea, ECG QT prolonged, headache, stomatitis, hyponatremia, and alopecia.

### 1.1.3.2. Phase 3 Studies

The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline *BRCA* mutation breast cancer subjects ([PR-30-5010-C](#); BRAVO) and to platinum-sensitive ovarian cancer subjects ([PR-30-5011-C](#); NOVA). Treatment with niraparib has been generally well tolerated. Refer to the Investigator's Brochure for more information.

### 1.1.4. Risks and Benefits

The potential benefit of niraparib treatment for patients with cancer is tumor regression.

Nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation ([Section 1.1.3.1](#)). The Investigator should monitor subjects closely for these AEs.

As Phase 1 studies have shown that niraparib is safe and well tolerated, the potential benefits outweigh the potential risks.

When taking niraparib, caution should be used when also taking medications that are inducers of cytochrome P450 1A2 (CYP1A2) or inhibitors or inducers of P-glycoprotein (P-gp; [Section 5.2](#)). The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs ([Section 5.2](#)).

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib.

Guidance on monitoring subjects for new events of MDS/AML and the follow-up of subjects with suspected MDS/AML is provided in [Section 3.4](#) and [Section 8.1.8](#).

## **1.2. Rationale for Current Study**

This is an open-label study with 2 parts, plus an extension study following completion of Parts 1 or 2, that is being conducted in approximately 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) with cancer to examine the absorption, metabolism, excretion, and absolute bioavailability of niraparib. This study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

The oral bioavailability of niraparib has been determined in rats and dogs ([Section 1.1.2](#)), but has yet to be determined in human subjects, including those with cancer. Therefore, this study will examine the absolute oral bioavailability of niraparib and the absorption, metabolism, excretion, and mass balance of oral [ $^{14}\text{C}$ ]-niraparib in subjects with cancer.

The oral dose of niraparib used in this study is 300 mg, which is the maximum tolerated dose of niraparib. A total of 144 subjects have been treated with niraparib up to 400 mg QD PO in Phase 1 studies, and the 300-mg daily dose of niraparib is considered safe and generally well tolerated ([IB](#)). The 300-mg daily dose of niraparib is currently being administered in 2 Phase 3 studies ([Section 1.1.3.2](#)).

This study will be the first-in-human administration of the IV formulation of niraparib. Data from the nonclinical studies did not demonstrate any safety issues that would preclude testing of IV niraparib in humans, and a microdose (100  $\mu\text{g}$ ) of niraparib is being administered in the current study.

## **2. STUDY OBJECTIVES AND PURPOSE**

### **2.1. Primary Objective**

- To determine the absolute bioavailability of niraparib by using an IV niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer.

### **2.2. Secondary Objectives**

- To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer.
- To evaluate the safety and tolerability of niraparib in subjects with cancer.

### 3. INVESTIGATIONAL PLAN

#### 3.1. Overall Study Design

This is an open-label study with 2 parts, plus an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP).

**Part 1:** The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center on Day 1 at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of  $100 \mu\text{g}$  niraparib, containing approximately  $1 \mu\text{Ci}$  of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center on Day 1 at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately  $100 \mu\text{Ci}$  of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu\text{Ci}$  of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. Participation may continue beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm 24$  hours of the final urine or fecal sample ([Section 7.2](#) and [Section 7.3](#)).

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments. No fasting period is required during the extension study. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject ([Section 3.4](#)). Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

The schedule of assessments for Part 1, Part 2, and the extension study are presented in [Table 1](#), [Table 2](#), and [Table 3](#), respectively.

### 3.2. Number of Subjects

There will be 6 subjects in Part 1 of the study and 6 subjects in Part 2 of the study. Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

### 3.3. Treatment Assignment

At the Screening Visit, subjects will be offered the option to participate in either Part 1 or Part 2 of the study until 1 part of the study is fully enrolled, at which time subjects can only be screened for the remaining part of the study, or for future replacements ([Section 4.4.1](#)). Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

### 3.4. Dose Adjustment Criteria

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject. Treatment must be interrupted for any nonhematologic National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.02; HHS 2009) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days of dose interruption, at the Investigator's discretion the subject may restart treatment with niraparib, but with a dose level reduction according to [Table 5](#) if prophylaxis is not considered feasible. Upon re-challenge, if the event recurs at a similar or worse grade, then treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted.

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 28-day dose interruption period, and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

**Table 5: Niraparib Dose Reductions for Nonhematologic Toxicities**

Event <sup>a</sup>	Dose <sup>b</sup>
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE $\geq$ 28 days	Discontinue study drug

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; QD, once a day; SAE, serious adverse event.

<sup>a</sup> Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject.

<sup>b</sup> Dose not to be decreased below 100 mg QD.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts, as outlined in [Table 6](#).

**Table 6: Niraparib Dose Modification/Reduction for Hematologic Toxicities**

Event	Dose Modification
Platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at the same dose or a reduced dose based on clinical judgment.
Second occurrence of platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count $< 75,000/\mu\text{L}^a$	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophils $< 1000/\mu\text{L}$	Study drugs must be interrupted until neutrophil counts are $\geq 1500/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin $\leq 8 \text{ g/dL}$	Study drugs must be interrupted until hemoglobin is $\geq 9 \text{ g/dL}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviation: CBC, complete blood count.

<sup>a</sup> For subjects with a platelet count  $\leq 10,000/\mu\text{L}$ , a prophylactic platelet transfusion per guidelines may be considered (Schiffer et al., 2001; Slichter, 2007). For subjects taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as  $\leq 20,000/\mu\text{L}$

If dose interruption or modification is required at any point during the study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for CBC will be required for an additional 28 days after the AE has been resolved to the specified levels, after which monitoring every 28 days may resume. Weekly blood draws for CBC can be collected either at the study center or local laboratories. If the hematologic toxicity has not recovered to the specified levels within 28 days of the dose interruption period and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

Any subject requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed.

The subject must be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, then the subject must permanently discontinue study treatment.

For major surgery while on treatment, up to 28 days of drug interruption is allowed.

Once the dose of study drug has been reduced, any re-escalation must be discussed with the Medical Monitor.

All dose interruptions and reductions (including any missed doses) and the reasons for the interruptions and reductions will be recorded in the electronic case report form (eCRF).

### **3.5. Criteria for Study Termination**

If in the opinion of the Investigator or Sponsor there is reasonable or sufficient cause, this study may be prematurely terminated at any time. Written notification documenting the reason for study termination will be provided to the Investigator or Sponsor by the terminating party.

Circumstances that may warrant termination include study center performance issues, a potential new finding with the study drug, or changes in the development program. See [Section 4.4](#) for subject withdrawal criteria. Additional circumstances include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enroll subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of study drug

Should the study be stopped prematurely, all study materials must be returned to the Sponsor or be disposed of according to the Sponsor's specifications.

## 4. SELECTION AND WITHDRAWAL OF SUBJECTS

### 4.1. Subject Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has a histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy or have progressed despite standard therapy; or has refused standard therapy (or for which no standard therapy exists); and subject may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - Platelets  $\geq 150,000/\mu\text{L}$
  - Hemoglobin  $\geq 9 \text{ g/dL (5.6 mM)}$
  - Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 4.3](#)).
8. Subject is able to take oral medications.
9. Subject must agree to blood samples during screening and at the end of treatment for cytogenetic analysis

### 4.2. Subject Exclusion Criteria

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing >20% of the bone marrow.
2. Subject has persistent >Grade 2 toxicity from prior cancer therapy.
3. Subject has any known, persistent (>4 weeks) ≥Grade 3 hematological toxicity or fatigue from prior cancer therapy.
4. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
5. Subject has known hypersensitivity to the components of niraparib.
6. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
7. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
8. Subject received (or is anticipated to receive) a platelet transfusion within 4 weeks of study drug administration.
9. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study, interfere with the subject’s participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
10. Subject has any known history of myelodysplastic syndrome (MDS) or a pre-treatment cytogenetic testing result at risk for a diagnosis of MDS/acute myeloid leukemia (AML).
11. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
12. Subject is immunocompromised with an active event and is being treated with medications.
13. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
14. Subject has a corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.

15. Subject is receiving concomitant medications that prolong QTc and is unable to discontinue use for the duration of the study ([Appendix 16.1](#)).
16. Subject is starting chemotherapy within 3 weeks of study drug administration.
17. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
18. Subject has a history of illicit drug use.
19. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
20. Subject is currently participating in another clinical study and has received an investigational drug, or has participated in a clinical study and has received an investigational drug within 21 days of study drug administration.
21. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months prior to study drug administration (for subjects participating in Part 1) or within 30 days prior to study drug administration (for subjects participating in Part 2).

#### **4.3. Restrictions During Study**

Restrictions during the study include the following:

1. If sexually active, subjects of reproductive potential and their partners must agree to the use of 2 of the following highly effective forms of contraception throughout their participation in the study and for 90 days after the last dose of study drug:
  - Condom with spermicide and one of the following:
    - Oral contraceptive or hormonal therapy (eg, hormone implants)
    - Placement of an intrauterine device

Acceptable nonhormonal birth control methods include the following:

- Total sexual abstinence
- Vasectomized sexual partner and use of a male condom, with subject assurance that partner received postvasectomy confirmation of azoospermia
- Tubal occlusion and use of a male condom with spermicide
- Intrauterine device and use of a male condom with spermicide

Acceptable hormonal birth control methods with use of a male condom with spermicide include the following:

- Etonogestrel implants (eg, Implanon®, Norplant®)
- Normal and low dose combined oral contraceptive pills
- Norelgestromin/ethynodiol transdermal system

- Intravaginal device (eg, ethinyl estradiol and etonogestrel)
  - Cerazette® (desogestrel), which is currently the only highly efficacious progesterone-based pill
2. No other anticancer therapy is permitted during the course of study treatment for any subject. If the subject discontinues study drug, this restriction no longer applies. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.
  3. Prophylactic cytokine (granulocyte colony-stimulating factor) administration should not be given in the first cycle of the extension study but may be administered in subsequent cycles according to local guidelines.
  4. An increased risk of infection with the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown, so live virus and bacterial vaccines should not be administered to subjects in the study.
  5. Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to receiving study drug and/or within 6 hours after receiving study drug.
  6. Subjects who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.
  7. Blood transfusions within the first 3 days post study drug administration are permissible if the blood transfusion is <500 mL/day.
  8. Subjects are not to take medications known to prolong QTc ([Section 16.1](#)) while participating in the study.

#### **4.4. Subject Withdrawal Criteria**

A subject may be discontinued from treatment or from the study for the following reasons:

- AE
  - For the extension study only, a treatment-related CTCAE Grade 3 or 4 AE that has not reverted to CTCAE Grade 1 or less within 28 days of dose interruption. At the Investigator's discretion, following dose interruption (no longer than 28 days), subjects may be considered for dose reductions ([Section 3.4](#)), providing they have not already undergone the maximum number of 2 dose reductions allowed. If a CTCAE Grade 3 or 4 AE recurs upon re-challenging with study drug at the lowest allowable dose, the subject must permanently discontinue treatment.
- Unacceptable toxicity
  - For the extension study only, if the subject experiences a dose interruption or modification because of a hematologic toxicity and the platelet count has not reverted to  $\geq 100,000/\mu\text{L}$  within 28 days of dose interruption, the subject should be discontinued.

- Severe noncompliance with the protocol, as judged by the Investigator and/or Sponsor.
- Subject becomes pregnant
- It is in the best interest of the subject, as judged by the Investigator and/or Sponsor
- Subject withdraws consent
- Sponsor decision to terminate study
- For the extension study only, disease progression and/or clinical criteria per standard of care

Subjects who discontinue from treatment will continue to receive follow-up safety assessments (see [Section 8](#)) as part of the study for 30 days from the last dose, unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the subject, who is at any time and for any reason free to discontinue their participation in the study, without prejudice to further treatment
- Death
- Loss to follow-up

If a subject is lost to follow-up or withdraws from study treatment, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.

#### **4.4.1. Replacement of Subjects**

After consultation between the Sponsor and the Principal Investigator (PI), enrollment may be extended to replace subject(s) discontinued during the study. Replacement subjects will be assigned the next available dosing number for the part of study in which the discontinued subjects were enrolled.

## 5. TREATMENT OF SUBJECTS

### 5.1. Description of Study Drug

The investigational products that will be used in this study are summarized in [Table 7](#).

**Table 7: Investigational Product**

Investigational Product			
<b>Product Name</b>	niraparib	[ <sup>14</sup> C]-niraparib IV solution	[ <sup>14</sup> C]-niraparib
<b>Dosage Form</b>	100-mg capsules	sterile solution for IV administration	capsules
<b>Unit Dose</b>	300 mg (3 × 100-mg capsules)	100 µg (1 µCi total radioactivity)	300 mg (3 × 100-mg capsules, 3 x 33.3 µCi of radioactivity [100 µCi total radioactivity])
<b>Route of Administration</b>	oral	IV	oral
<b>Study Phase Taken</b>	Part 1 and Extension	Part 1	Part 2

Abbreviation: IV, intravenous.

### 5.2. Prior and Concomitant Medications

Any medication the subject takes during the study other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication.

All prior and concomitant medications will be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Known prior medications that exclude a subject from participating in the study are described in the Exclusion Criteria ([Section 4.2](#)). Prohibited concomitant medications are described in [Section 4.3](#). Additionally, niraparib has potential to induce CYP1A2. Therefore, subjects should be advised to use caution when taking medications that are also inducers of CYP1A2. Examples of CYP1A2 inducers include montelukast, phenytoin, moricizine, omeprazole, and phenobarbital ([HHS 2012](#)). Niraparib is a substrate for P-gp; therefore, subjects should be advised to use caution when taking medications that are inhibitors or inducers of P-gp. Examples of P-gp inhibitors include the following ([HHS 2012](#)): amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil. Examples of P-gp inducers include the following ([HHS 2012](#)): avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir-ritonavir. Permitted anti-nausea medications are dexamethasone, aprepitant, and granisetron.

Subjects must not be receiving medications that prolong QTc at Screening and for the duration of the study ([Section 16.1](#))

The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs.

### **5.3. Treatment Compliance**

The study staff will maintain an ongoing record of the dispensing and administration of study drug for each subject. For the extension study, subjects will be instructed to return any unused study drug to the study center during their visit on the first day of each cycle or at EOT. Drug accountability will be performed on capsules dispensed versus returned to the study center at each visit and the number of days since the last visit.

### **5.4. Randomization and Blinding**

Subjects will not be randomly assigned and instead may choose in which part of the study to participate ([Section 3.3](#)). This is an unblinded study.

## 6. STUDY DRUG MATERIALS AND MANAGEMENT

### 6.1. Study Drug

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor.

### 6.2. Study Drug Packaging and Labeling

Niraparib 100-mg capsules (unlabeled active pharmaceutical ingredient) will be packed in high-density polyethylene bottles with child-resistant closures. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-subject-specific.

For the extension study, each dosing container will contain a sufficient number of capsules for 1 treatment cycle. Niraparib will be dispensed to subjects on Day 1 of every cycle of the extension study.

The IV solution and oral capsules will be prepared for dosing by Quotient Clinical from [<sup>14</sup>C]-niraparib active pharmaceutical ingredient following Good Manufacturing Practices. Information on the preparation, packaging, and labeling of the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity per 300-mg dose) of niraparib can be found in the investigational medicinal product dossier.

### 6.3. Study Drug Storage

All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed to the subjects, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

Information for storing the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity) of niraparib can be found in the investigational medicinal product dossier.

### 6.4. Study Drug Administration

For Part 1, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For Part 2, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3\text{ }\mu\text{Ci}$  of radioactivity]), on Day 1 after an overnight fast of at least 10 hours.

Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For the extension study, 300 mg of niraparib ( $3 \times 100\text{-mg}$  capsules, unlabeled active pharmaceutical ingredient) will be administered orally QD until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)); dose interruptions and reductions will be allowed based on treatment side effects ([Section 3.4](#)). No fasting period is required during the extension study. Subjects will be instructed to take the niraparib dose at the same time of day, preferably in the morning. The first dose will be administered at the study center. Subjects must swallow and not chew the capsules, and the consumption of water is permissible. On days of study visits (eg, Cycle 1, Day 1, 8, 15, and 22; Cycle n, Day 1), subjects should refrain from taking niraparib until after clinical assessments are performed.

## **6.5. Study Drug Accountability**

The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes the subject number, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as “returned” and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. When the study monitor visits the site, he or she will reconcile the drug accountability log with the products stored in the pharmacy.

## **6.6. Study Drug Handling and Disposal**

After receiving Sponsor approval in writing, the study center is responsible for returning all unused or partially used study drug to Sponsor or a designated third party or for preparing the study drug for destruction at the investigational study center.

## 7. PHARMACOKINETIC ASSESSMENTS

Subjects will undergo the following procedures according to the schedule of assessments presented in [Table 1](#), [Table 2](#), and [Table 3](#).

### 7.1. Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling

For Part 1, blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [within 1 min prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 [within 1 min post-infusion], 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For Part 2, blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose). Participation in Part 2 of the study may extend beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm 24$  hours of the final urine or fecal sample. ([Section 7.2](#) and [Section 7.3](#)).

For Part 2, blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

The exact time that each sample is collected will be recorded by the study center, regardless of whether the sample is collected within the specified windows. A detailed description of the blood sample schedule and aliquot collection is included in [Table 8](#) and [Table 9](#) for Parts 1 and 2, respectively. Blood samples that will be used to measure the plasma concentration of [ $^{14}\text{C}$ ]-niraparib with accelerator mass spectrometry (AMS) in Part 1 will be transferred for analysis. Refer to the laboratory manual for further details on sample handling and shipping.

**Table 8: Part 1 Blood Sample Schedule and Aliquot Collection**

Day From Oral Dose	Time From Oral Dose	Time From Start of IV Infusion (hour)	Blood Samples for AMS Plasma Analysis of IV Dose (mL) <sup>a</sup>	Blood Samples for LC-MS/MS Plasma Analysis of Oral Dose (mL) <sup>b</sup>	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	—	2	2	8
	1 hr [±2 min]	—	—	2	2
	1.5 hr [±2 min]	—	—	2	2
	2 hr [within 1 min prior to IV infusion]	0 <sup>c</sup>	2	2	8
	2.125 hr [±1 min] <sup>d</sup>	0.125 <sup>c</sup>	2	—	4
	2.25 hr [within 1 min post-infusion] <sup>e</sup>	0.25 <sup>c</sup>	2	—	4
	2.33 hr [±1 min] <sup>f</sup>	0.33 <sup>c</sup>	2	—	4
	2.66 hr [±1 min] <sup>g</sup>	0.66 <sup>c</sup>	2	—	4
	3 hr [±2 min]	1 <sup>c</sup>	2	2	8
	4 hr [±5 min]	2 <sup>c</sup>	2	2	8
	6 hr [±5 min]	4 <sup>c</sup>	2	2	8
	12 hr [± 15 min]	10 <sup>c</sup>	2	2	8
2	24 hr [±1 hr]	22 [±1]	2	2	8
3	48 hr [±2 hr]	46 [±2]	2	2	8
4	72 hr [±4 hr]	70 [±4]	2	2	8
5	96 hr [±4 hr]	94 [±4]	2	2	8
7	144 hr [±4 hr]	142 [±4]	2	2	8
9	192 hr [±8 hr]	190 [±8]	2	2	8
11	240 hr [±12 hr]	238 [±12]	2	2	8
13	288 hr [±12 hr]	286 [±12]	2	2	8
15	336 hr [±12 hr]	334 [±12]	2	2	8
22	504 hr [±12 hr]	502 [±12]	2	2	8

Abbreviations: AMS, accelerator mass spectrometry; IV, intravenous; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

<sup>a</sup> These samples will include 1 sample for AMS analysis (2 mL), and 1 sample that will be used as either a back-up sample for AMS analysis or potentially for LC-MS/MS analysis (2 mL).

<sup>b</sup> These samples will include 1 sample for LC-MS/MS analysis (2 mL) and 1 back-up sample (2 mL).

<sup>c</sup> Refer to Time From Oral Dose column for collection windows for the 0-10 hr Time From Start of IV Infusion.

<sup>d</sup> 2 hr 7.5 min

<sup>e</sup> 2 hr 15 min

<sup>f</sup> 2 hr 20 min

<sup>g</sup> 2 hr 40 min

**Table 9: Part 2 Blood Sample Schedule and Aliquot Collection**

Day	Time From Oral Dose	Blood Samples for LC-MS/MS Plasma Analysis <sup>a</sup> (mL)	Blood Sample for LSC Plasma Analysis (mL)	Blood Sample for LSC Whole Blood Analysis (mL)	Metabolite Profiling LC-MS/LC-MS/MS (mL)	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	2	2	2	2	10
	1 hr [ $\pm 2$ min]	2	2	2	2	10
	1.5 hr [ $\pm 2$ min]	2	2	2	—	8
	2 hr [ $\pm 2$ min]	2	2	2	2	10
	3 hr [ $\pm 2$ min]	2	2	2	2	10
	4 hr [ $\pm 5$ min]	2	2	2	—	8
	6 hr [ $\pm 5$ min]	2	2	2	2	10
	12 hr [ $\pm 15$ min]	2	2	2	2	10
2	24 hr [ $\pm 1$ hr]	2	2	2	2	10
3	48 hr [ $\pm 2$ hr]	2	2	2	2	10
4	72 hr [ $\pm 4$ hr]	2	2	2	2	10
5	96 hr [ $\pm 4$ hr]	2	2	2	2	10
6	120 hr [ $\pm 4$ hr]	2	2	2	2	10
8	168 hr [ $\pm 4$ hr]	2	2	2	2	10
11	240 hr [ $\pm 12$ hr]	2	2	2	2	10
15	336 hr [ $\pm 12$ hr]	2	2	2	2	10
22	504 hr [ $\pm 12$ hr]	2	2	2	2	10

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> These samples will include 1 sample for analysis (2 mL), and 1 back-up sample (2 mL).

## 7.2. Urine Sample Collection

Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be

quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. The discontinuation of urine sample collections will be based on:

1. If the total radioactivity in the Day 14 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then urine samples will be collected every 24 hours through Day 21.
2. If the total radioactivity in the Day 21 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then urine samples will continue to be collected every 24 hours.
3. Urine sample collection will stop at the end of Day 21 if the recovered radioactivity is  $<1\%$  (per 24 hours) for the 2 consecutive days prior to Day 21 (Days 19 and 20). If this is not the case, then collection will stop as soon as the recovered radioactivity is  $<1\%$  (per 24 hours) for 2 consecutive days after Day 21.

A detailed description of the urine sample schedule and the aliquot collection is included in Table 10. Refer to the laboratory manual for further details on sample storage conditions.

**Table 10: Urine Sample Schedule and Aliquot Collection**

Day	Interval (hour)	Niraparib Concentration LC-MS/MS Analysis (mL)	Radioactivity LSC Analysis (mL)	Metabolite Profiling LC-MS /LC-MS/MS (mL)	Total Urine Sample Volume (mL)
1	0 (predose)	$2 \times 3$	1	$3 \times 10$	37
	0-12				
	12-24				
2	24-36				
	36-48				
3	48-72				
4	72-96				
5	96-120				
6	120-144				
7	144-168				
8	168-192				
9	192-216				
10	216-240				
11	240-264				
12	264-288				
13	288-312				

**Table 10: Urine Sample Schedule and Aliquot Collection (Continued)**

Day	Interval (hour)	Niraparib Concentration LC-MS/MS Analysis (mL)	Radioactivity LSC Analysis (mL)	Metabolite Profiling LC-MS /LC-MS/MS (mL)	Total Urine Sample Volume (mL)
14	312-336				
15 <sup>a</sup>	336-360				

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> See above for collection stop criteria.

### 7.3. Fecal Sample Collection

Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. The discontinuation of fecal sample collections will be based on:

1. If the total radioactivity in the Day 14 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then fecal samples will be collected every 24 hours through Day 21.
2. If the total radioactivity in the Day 21 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then fecal samples will continue to be collected every 24 hours.
3. Feces sample collection will stop at the end of day Day 21 if the recovered radioactivity is  $<1\%$  (per 24 hours) for the 2 consecutive days prior to Day 21 (Days 19 and 20). If this is not the case, then collection will stop as soon as the recovered radioactivity is  $<1\%$  (per 24 hours) for 2 consecutive days after Day 21.

A detailed description of the fecal sample schedule and the aliquot collection is included in Table 11. Refer to the laboratory manual for further details on sample storage conditions.

**Table 11: Fecal Sample Schedule and Aliquot Collection**

Day	Time (hour)	Aliquot Collection
1	0 (predose)	Fecal samples will be processed per stool and analyzed in 24-hour intervals.
	0-24	
2	24-48	
3	48-72	
4	72-96	
5	96-120	
6	120-144	

**Table 11: Fecal Sample Schedule and Aliquot Collection (Continued)**

Day	Time (hour)	Aliquot Collection
7	144-168	
8	168-192	
9	192-216	
10	216-240	
11	240-264	
12	264-288	
13	288-312	
14	312-336	
15 <sup>a</sup>	336-360	

Abbreviation: LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> See above for collection stop criteria.

#### 7.4. Sample Analysis

Analysis of blood, urine, and fecal samples includes the following:

- **Blood:** Blood samples will be analyzed for the plasma concentrations of niraparib and the major metabolite (M1) using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Part 1 blood samples will be analyzed for the plasma concentration of [<sup>14</sup>C]-niraparib using AMS. Part 2 blood samples will be analyzed for the whole blood and plasma concentrations of [<sup>14</sup>C]-niraparib using liquid scintillation counting (LSC). Part 2 plasma blood samples will be analyzed for metabolite profiling and identification using high resolution liquid chromatography-mass spectrometry (LC-MS), in combination with LC-MS/MS (including ion trap instruments). A quantitative LC-MS/MS method will be established for niraparib and the major carboxylic acid metabolite.
- **Urine:** Radioactivity content in urine samples will be determined by LSC. The concentration of niraparib and the major metabolite (M1) will be determined with LC-MS/MS. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).
- **Fecal:** Radioactivity content in fecal samples will be determined by LSC. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).

Pharmacokinetic parameters of interest include the following:

- **Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters: C<sub>max</sub>; time to reach C<sub>max</sub> (T<sub>max</sub>); and AUC from time 0 to the last quantifiable concentration (AUC<sub>0-last</sub>); and if the data allow: AUC from time 0 to infinity (AUC<sub>0-inf</sub>); apparent oral volume of distribution (Vd/F); apparent oral

clearance (CL/F); and half-life ( $t_{1/2}$ ). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

- **Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ ,  $Vd/F$ ,  $CL/F$ , and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$  (day), and total amount of drug excreted in the urine,  $A_e$  (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption ( $f$ ), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.

## **8. ASSESSMENT OF SAFETY**

Subjects will undergo the following procedures according to the schedule of assessments presented in [Table 1](#), [Table 2](#), and [Table 3](#).

### **8.1. Safety Parameters**

#### **8.1.1. Demographic and Baseline Characteristics**

The following demographic information will be documented during the Screening Visit for Parts 1 and 2:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (Asian, Black, Caucasian, Other, Unknown)

The following baseline characteristics will be documented during the Screening Visit for Parts 1 and 2:

- History of drug, alcohol, or other substance abuse
- History of psychiatric illness
- Smoking history

#### **8.1.2. Medical History and Cancer History**

Major medical history will be collected during the Screening Visit for Parts 1 and 2. Medical history will be obtained by interviewing the subjects or by reviewing their medical records.

Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis. CT scans should be performed per standard of care. If the subject discontinues due to disease progression, then the CT scan closest to the time of progression (EOT) should also be provided.

The following will be documented for cancer history:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Tumor grade
- Date of start of first treatment
- Agents used in first treatment
- Date of last dose of first treatment
- Date of relapse for each treatment

### **8.1.3. Prior and Concomitant Medications**

For prior medications, subjects will be asked during the Screening Visit for Parts 1 and 2 what medications they have taken during the last 30 days. All concomitant medications will be recorded from the time the subject signs the informed consent form (ICF) through completion of the study.

### **8.1.4. Vital Signs**

Blood pressure, pulse rate, and aural (tympanic) temperature will be measured while the subject is in the supine position at every visit that the subject is at the study center (see [Table 1](#), [Table 2](#), and [Table 3](#) for time points) after the subject has been resting for approximately 2 minutes. Vital signs will be collected prior to study drug administration on Day 1.

### **8.1.5. Weight, Height, and Body Mass Index**

Height (cm) and weight (kg) will be measured without shoes during the Screening Visit for Parts 1 and 2, and body mass index ( $\text{kg}/\text{m}^2$ ) will be calculated. For Parts 1 and 2, weight will also be measured at the Day 22 Visit. For the extension study, weight will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

### **8.1.6. Physical Examination**

The physical examination includes an assessment of general appearance and a review of body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems).

For Parts 1 and 2, the physical examination will be performed at the Screening Visit and at the Day 22 Visit. For the extension study, the physical examination will be performed at the Cycle 1/Day 1 Visit, Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

### **8.1.7. Electrocardiogram**

For Parts 1 and 2, the 12-lead ECG will be performed during the Screening Visit, the Day 1 Visit (predose and 2 hours postdose), the Day 22 Visit, and at EOT. For the Extension Study, the 12-lead ECG will be performed at Cycle 1 Day 1, at the Day 1 Visit (predose and 2 hours postdose) for each cycle during the extension study, and at EOT. Subjects will be in the supine position and resting for approximately 2 minutes before ECGs are recorded. For the measurement of QTc prolongation at the Screening Visit, results will include a mean of triplicate ECG readings (3 readings in rapid succession not more than 2 minutes apart).

### **8.1.8. Clinical Laboratory Assessments**

Laboratory assessments will be performed by the local laboratory at the study center. Blood samples should be drawn prior to study drug administration.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the study center. The Investigator or designee will indicate whether or not the value is of clinical significance and whether or not the subject requires intervention or further monitoring. Clinical significance will be defined as that requiring medical intervention. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality is found in the samples taken during the study, it should be recorded as an AE, and the subject will be followed until the test has normalized or stabilized.

For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization (WHO) criteria (Vardiman 2009) and other sample testing reports related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the subject's study file.

#### **8.1.8.1. Parts 1 and 2 Laboratory Assessments**

Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio.

Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

Assessments will be conducted at the Screening Visit (must be collected within 72 hours prior to dosing), Day 15, and the Day 22 Visit.

For the hematology assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **8.1.8.2. Extension Study Laboratory Assessments**

The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. The CBC will be conducted at the Screening Visit (drawn within 72 hours prior to study drug administration), Days 8, 15, and 22 of Cycle 1; Day 1 of every new cycle; and EOT.

Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. These assessments will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and EOT.

For the CBC, 3 mL of blood will be collected. For the coagulation assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **8.1.9. Laboratory Screenings**

#### **8.1.9.1. Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Screening**

Testing for HBV, HCV, and HIV will only be performed during the Screening Visit for Parts 1 and 2 if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

#### **8.1.9.2. Pregnancy Screen**

A serum pregnancy test will be performed for women of childbearing potential according to standard local procedures during the Screening Visit for Parts 1 and 2. All subjects who do not continue to the extension study will have a serum pregnancy test prior to study exit. Subjects who continue to the extension study will have a serum pregnancy test at the screening visit and at treatment discontinuation for the extension study. A urine pregnancy test will be performed every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.).

### **8.1.10. Eastern Cooperative Oncology Group Performance Scale**

The ECOG performance scale assesses the subject's general well-being and activities of daily life ([Appendix 16.2](#)). To be eligible for enrollment into this study, subjects must have an ECOG performance status of 0 to 2 during the Screening Visit for Parts 1 and 2. ECOG assessments will be conducted at the Parts 1 and 2/Day 22 Visit for subjects who are not enrolling in the extension study. The ECOG performance status will be reassessed during the extension study at the Screening Visit, the Day 1 Visit for Cycle 2 and each subsequent cycle, and at EOT. The same observer should assess performance status each time.

### **8.1.11. Blood and Tissue Samples**

Whole blood samples will be collected for all subjects during screening and at EOT. Some samples will be used to determine eligibility per MDS/AML-related criteria (see [Section 4](#)). These test results must be received prior to randomization. For all eligible subjects, remaining samples will be stored. Stored samples will be evaluated for mutations of selected myeloid-

associated genes if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). Details on blood and tissue sample collection can be found in the Laboratory Manual.

### **8.1.12. New Malignancies**

Although overall survival is not an endpoint in this study, to monitor for MDS/AML and the occurrence of new malignancies, new malignancy information will be collected for all subjects via telephone every 90 days following the treatment discontinuation visit (subjects in the extension study only).

## **8.2. Adverse and Serious Adverse Events**

### **8.2.1. Definition of Adverse Events**

#### **8.2.1.1. Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be documented.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study treatment has been administered.

#### **8.2.1.2. Disease Progression**

The event of disease progression is an efficacy criterion and is therefore not considered an AE. If AEs/SAEs occur in relation to disease progression, then the AEs/SAEs must be reported per AE/SAE reporting requirements described in [Section 8.6](#).

#### **8.2.1.3. Serious Adverse Event**

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:

- Results in death

- Is life-threatening
  - This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability or incapacity
  - Is a congenital anomaly or birth defect
  - Is an important medical event(s)
- An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, disease progression, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

A distinction should be drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

#### **8.2.1.4. Submission of Expedited Reports to Regulatory Authority, Sites, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

Per regulatory requirements, if an SAE report is required to be submitted to a Regulatory Authority a copy of this report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigators/site. TESARO or its designee will submit a copy of the report to their respective IRB or IEC.

### **8.3. Relationship to Study Drug**

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- **Related:** A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by

concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.

- Likely related: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.
- Unlikely to be related: A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.
- Unrelated: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

#### **8.4. Recording Adverse Events**

AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New AEs and SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see [Table 1](#), [Table 2](#), and [Table 3](#) for schedules of events) or until new anticancer therapy is initiated. All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center.

Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the above SAE reporting process.

Abnormal laboratory values that constitute an AE or SAE must be collected. Investigators should assess the severity of AEs according to CTCAE ([HHS 2009](#)).

In general, CTCAE version 4.02 severity grades are the following:

- Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under [Section 8.2.1.3](#). An AE of severe intensity may not be considered serious.

## 8.5. Reports of Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report notification form and reported to the Sponsor.

Pregnancies occurring in subjects enrolled in a study or in a female partner of a male subject must be reported and followed to outcome. The Investigator is responsible for documenting the course and outcome of any pregnancy that occurs while a subject is enrolled in the study and any pregnancy that occurs within 90 days after a subject's last dose.

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions.

Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see [Section 8.6](#)).

The investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The Investigator should follow-up with the subject or the subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs after the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor, or designee, within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs.

## PREGNANCY CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

### 8.6. Reporting Adverse Events

The Investigator must report any SAE within 24 hours of becoming aware of the event. SAEs must be reported using the following contact information:

## SAE REPORTING CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report Form must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the subject's personal identifiers (eg, subject name, medical record number) removed according to local regulations. The Investigator must sign and date all SAE forms.

*The minimum information required for an initial SAE report is:*

- Name of person sending the report (ie, name, address of Investigator)
- Subject identification (screening/randomization number, initials, NOT subject name)
- Protocol number
- Description of SAE
- Causality assessment

In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be

recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information.

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## **9. STATISTICS**

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined in this section. Any deviations from the planned analyses will be described in the final integrated clinical study report.

### **9.1. General Considerations**

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum value, and maximum value). Categorical data will be summarized using counts and percentages. All data will be listed in data listings.

### **9.2. Study Population**

#### **9.2.1. Subject Disposition**

The number and percentage of subjects who enter and complete the study will be presented by group (ie, Part 1 subjects, Part 2 subjects, and extension study subjects). Subjects who fail to complete the study will be summarized and categorized by reason for termination (lost to follow-up, AE, etc.). In addition, the numbers of subjects in each analysis set will be summarized by group

#### **9.2.2. Demographic Information and Baseline Characteristics**

Demographics and baseline characteristics will be summarized descriptively by group and will be summarized for each of the defined analysis sets.

#### **9.2.3. Prior and Concomitant Medications**

Medications will be coded according to the current version of the World Health Organization Drug Dictionary. Prior and concomitant medications will be summarized descriptively by group.

#### **9.2.4. Protocol Deviations**

Protocol deviations will be listed by subject and a summary of significant protocol deviations by type will be produced.

#### **9.2.5. Analysis Populations**

**Safety Population:** All subjects who received study drug

**Pharmacokinetic Population:** All subjects who received study drug and provide adequate PK samples to calculate PK parameters

## **9.3. Safety Analyses**

### **9.3.1. Adverse Events**

AE terms will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing an event will be summarized

for each system organ class and preferred term by group. Likewise, AEs will also be tabulated according to intensity and relationship to study drug. Serious AEs, discontinuation due to AEs, and deaths will also be presented and listed separately, including the relationship to study drug.

### **9.3.2. Physical Examinations**

Physical examination findings will be summarized descriptively by group and by study visit. Individual data listings of physical examination findings will be presented for each subject.

### **9.3.3. Vital Signs**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for vital signs. Individual data listings of vital signs will be presented for each subject.

### **9.3.4. Electrocardiograms**

Observed values at baseline and changes from baseline will be summarized descriptively by group and study visit for the ECG parameters, including PR interval and QTc. Individual data listings of ECGs will be presented for each subject. Flags will be attached to QTc values of clinical significance. Individual data listings of clinically significant ECG parameters will also be presented for each subject.

### **9.3.5. Clinical Laboratory Assessments**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for the clinical laboratory results. Individual data listings of clinical laboratory results will be presented for each subject. Shift tables based on normal ranges will also be presented for select chemistry and hematology laboratory parameters. Flags will be attached to values outside of the laboratory's reference limits along with the PI's assessment of clinical significance. Clinically significant laboratory values will be summarized separately by group and study visit, and individual data listings of clinically significant laboratory results will also be presented for each subject.

## **9.4. Post-treatment Analyses**

Descriptive summary statistics will be used to summarize post study treatment data (ie, any new malignancy). In addition, the relationship between cytogenetic abnormalities and safety parameters may be explored.

## **9.5. Pharmacokinetic Analyses**

### **9.5.1. Part 1**

Plasma concentrations based on the radioactivity and mass spectrometry (MS) ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

### **9.5.2. Part 2**

Whole blood and plasma concentrations based on the radioactivity and MS ion intensity and, if appropriate, the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

### **9.6. Determination of Sample Size**

The sample size of 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) is not based on statistical considerations and instead represents a balance between the number of subjects exposed and accounts for interindividual variability. Enrollment may be extended to replace subjects discontinued during the study ([Section 4.4.1](#)).

### **9.7. Data Monitoring**

An external Data Safety Monitoring Board will not be established for this study. The Sponsor will monitor safety throughout the project through the following efforts:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of nonserious AEs as they are recorded in the eCRF or appear in the source documents at the study center
- Periodic teleconferences with the PI to share experiences and ensure communication

Findings discovered to have immediate implication for the management of subjects on study treatment will be communicated to the PI in the timeframe associated with unexpected and drug-related SAEs.

Safety surveillance will include routine monitoring of clinical laboratory results, physical examination findings, vital signs, AE reporting, and ECG monitoring.

## **10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **10.1. Study Monitoring**

Before the study center can enter a subject into the study, a representative of the Sponsor or a designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or a representative will have regular contacts with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented in eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met the criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### **10.2. Audits and Inspections**

Authorized representatives of the Sponsor, a regulatory authority, an IEC, or an IRB may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

### **10.3. Ethics Committee**

The PI must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study, including the subject ICF and recruitment materials, must be maintained by the PI and made available for inspection.

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## 11. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its representative may conduct a quality assurance audit. Refer to [Section 10.2](#) for more details regarding the audit process.

## **12. ETHICS**

### **12.1. Ethics Review**

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The PI must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### **12.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsor's policy on Bioethics.

### **12.3. Written Informed Consent**

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

## **13. DATA HANDLING AND RECORDKEEPING**

### **13.1. Inspection of Records**

The Sponsor or its representative will be allowed to conduct study center visits at the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **13.2. Retention of Records**

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **14. PUBLICATION POLICY**

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

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## 15. LIST OF REFERENCES

- Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009 Jul 30;114(5):937-51.
- Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245-51.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361(2):123-34.
- Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-61.
- Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res*. 2012;18(6):1726-34.
- Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-92.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
- Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19(5):1519-38.
- Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program*. 2007:172-8.
- TESARO, Inc. Niraparib. Investigator's brochure, Version 3.0. Waltham (MA); 2014. 115 p.
- Thompson JL and Crossman RR. Drug-induced QT prolongation. *US Pharm*. 2007;32(2):44-50.
- United States Department of Health and Human Services (HHS). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. 2009 [cited 30 Jan 2014]. Available from: [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE\\_4.02\\_2009-09-15\\_QuickReference\\_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf).
- United States Department of Health and Human Services (HHS), Food and Drug Administration, Center for Drug Evaluation and Research. Draft guidance. Drug interaction studies – Study design, data analysis, implications for dosing, and labeling recommendations. February 2012 [cited 04 Feb 2014]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>.
- CredibleMeds. Available at: <https://www.crediblemeds.org>

US Pharmacist. Drug-induced QT prolongation page. Available at:  
[http://www.uspharmacist.com/content/d/featured\\_articles/c/10396/](http://www.uspharmacist.com/content/d/featured_articles/c/10396/). Accessed 12 November 2013.

Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. *Ann Pharmacother*. 2013;47(10):1330-41.

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## 16. APPENDICES

### 16.1. Drugs Associated with QT Prolongation and Torsades de Pointes (TdP)

Table 12: Select Drugs Associated with QT prolongation and TdP

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Doxepin	Droperidol	Sumatriptan
Quinidine	Gatifloxacin		Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin		Thioridazine	Arsenic
Dofetilide	Clarithromycin		Ziprasidone	Dolasetron
Ibutilide	Erythromycin			Methadone
	Ketoconazole*			
	Itraconazole			

\*Topical use allowed for ketoconazole

## 16.2. Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Reference: [Oken et al, 1982](#)



## Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

EudraCT No: 2014-002011-41

Sponsor: TESARO, Inc.

1000 Winter Street, Suite 3300  
Waltham, MA 02451 USA

TESARO Medical Monitor:

PI [REDACTED] MD, MPH  
Senior Medical Director

Principal Investigator:

PI [REDACTED], MD, PhD  
PI [REDACTED]  
PI [REDACTED], NL

Contract Research Organization:

PPD  
929 North Front Street  
Wilmington, NC 28401 USA

Version of Protocol:

4.0

Original Final Protocol Date:

28 May 2014

Amendment 1:

04 December 2014

Amendment 2:

17 March 2015

Amendment 3:

11 September 2015

This clinical investigation will be conducted according to this clinical protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki (Version 2008), and with other applicable regulatory requirements.

### Confidentiality Statement

All information contained in this document is privileged and confidential to TESARO. Any distribution, copying, or disclosure is strictly prohibited without prior written approval by TESARO.

## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

### Declaration of the Principal Investigator

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

#### Principal Investigator

---

Name:

Title:

Institution:

---

Date

## SPONSOR SIGNATURE PAGE

### Declaration of Sponsor or Responsible Medical Expert

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

#### Sponsor Signatory

PI

PI

MD, PI, PH

Senior Medical Director

TESARO, Inc.

*16 Sept 2015*

Date

## SYNOPSIS

<b>Name of Sponsor/Company:</b> TESARO, Inc.	
<b>Name of Investigational Product:</b> Niraparib	
<b>Name of Active Ingredient:</b> Niraparib	
<b>Title of Study:</b> Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer (Protocol Number PR-30-5015-C)	
<b>Study Center(s):</b> A single study center in the Netherlands	
<b>Principal Investigator:</b> PI [REDACTED], MD, PhD	
<b>Investigators:</b> Not applicable	
<b>Studied Period (years):</b> Estimated date first subject enrolled: February 2015 Estimated date last subject completed: December 2015	<b>Phase of Development:</b> 1
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"><li>To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer</li></ul> <b>Secondary:</b> <ul style="list-style-type: none"><li>To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer</li><li>To evaluate the safety and tolerability of niraparib in subjects with cancer.</li></ul>	
<b>Methodology:</b> This is an open-label study with 2 parts, plus an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP). <b>Part 1:</b> The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration on Day 1. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling. <b>Part 2:</b> The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study	

center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu$ Ci of radioactivity ( $3 \times 100$ -mg capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3$   $\mu$ Ci of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. Participation in Part 2 of the study may extend beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm 24$  hours of the final urine or fecal sample.

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [ $3 \times 100$ -mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments. No fasting period is required during the extension study. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject ([Section 3.4](#)). Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

**Number of Subjects (planned):**

**Part 1:** 6 subjects

**Part 2:** 6 subjects

Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

**Diagnosis and Main Criteria for Inclusion:**

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has a histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy; or have progressed despite standard therapy; or

has refused standard therapy (or for which no standard therapy exists); and subject may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.

4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 150,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL} (5.6 \text{ mM})$
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 4.3](#)).
8. Subject is able to take oral medications.
9. Subject must agree to blood samples during screening and at the end of treatment for cytogenetic analysis.

**Exclusion Criteria:**

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>$ Grade 2 toxicity from prior cancer therapy.
3. Subject has any known, persistent ( $>4$  weeks)  $\geq$ Grade 3 hematological toxicity or fatigue from prior cancer therapy.
4. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
5. Subject has known hypersensitivity to the components of niraparib.
6. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
7. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava

- syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
8. Subject received (or is anticipated to receive) a platelet transfusion within 4 weeks of study drug administration.
  9. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
  10. Subject has any known history of myelodysplastic syndrome (MDS) or a pre-treatment cytogenetic testing result at risk for a diagnosis of MDS/acute myeloid leukemia (AML).
  11. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
  12. Subject is immunocompromised with an active event and is being treated with medications.
  13. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
  14. Subject has a corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.
  15. Subject is receiving concomitant medications that prolong QTc and is unable to discontinue use for the duration of the study ([Appendix 16.1](#)).
  16. Subject is starting chemotherapy within 3 weeks of study drug administration.
  17. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
  18. Subject has a history of illicit drug use.
  19. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
  20. Subject is currently participating in another clinical study and has received an investigational drug, or has participated in a clinical study and has received an investigational drug within 21 days of study drug administration.
  21. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months prior to study drug administration (for subjects participating in Part 1) or within 30 days prior to study drug administration (for subjects participating in Part 2).

**Investigational Product, Dosage and Mode of Administration:**

**Part 1:** Niraparib 300 mg (3 x 100-mg capsules) orally and [<sup>14</sup>C]-niraparib 100 µg (1 µCi total radioactivity) intravenously

**Part 2:** [<sup>14</sup>C]-niraparib 300 mg (3 x 100-mg capsules; 3 x 33.3 µCi radioactivity [100 µCi total radioactivity]) orally

**Extension study:** Niraparib 300 mg (3 x 100-mg capsules) orally

**Duration of Treatment:**

**Part 1:** Administration of a single oral dose, followed by a 15-minute IV infusion 2 hours after administration of the single oral dose

**Part 2:** Administration of a single oral dose

**Extension Study:** QD administration until treatment discontinuation

**Reference Therapy, Dosage and Mode of Administration:**

None.

**Criteria for Evaluation:**

**Pharmacokinetics:**

**Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters: maximum observed plasma concentration ( $C_{max}$ ); time to reach  $C_{max}$  ( $T_{max}$ ); and area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration ( $AUC_{0-last}$ ); and if the data allow: AUC from time 0 to infinity ( $AUC_{0-inf}$ ); apparent oral volume of distribution ( $Vd/F$ ); apparent oral clearance ( $CL/F$ ); and half-life ( $t_{1/2}$ ). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

**Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ ,  $Vd/F$ ,  $CL/F$ , and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$ (day), and total amount of drug excreted in the urine,  $A_e$ (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption ( $f$ ), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.

**Safety:**

Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.

**Statistical Methods:**

**Pharmacokinetics:**

For Part 1, plasma concentrations based on the radioactivity and mass spectrometry (MS) ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure. For Part 2, whole blood and plasma concentrations based on the radioactivity and MS ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

**Safety:**

All AEs will be listed and tabulated. Physical examination findings, vital signs, ECG parameters, and clinical laboratory results will be listed and summarized using descriptive statistics.

**Table 1: Schedule of Assessments: Part 1\***

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X												X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X <sup>c</sup>	X	X	X <sup>d</sup>	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>d</sup>	X												
Clinical laboratory assessment <sup>e</sup>	X <sup>f</sup>												X X
Serum pregnancy test (women of childbearing potential)	X												X
Electrocardiogram (12-lead) <sup>g</sup>	X		X										X
ECOG performance status	X												X <sup>h</sup>
Confirm diagnosis with CT scan <sup>i</sup>	X												
Subject confinement		X <sup>c</sup>	X	X	X	X							
Niraparib oral administration <sup>j</sup>			X										
[ <sup>14</sup> C]-niraparib IV infusion <sup>k</sup>			X										

**Table 1: Schedule of Assessments: Part 1\* (Continued)**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Pharmacokinetic blood sampling <sup>b</sup>			X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>m</sup>	X	X <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous

\*Note: No modifications have been made to Part 1 assessments for MDS/AML monitoring, as all Part 1 subjects had either exited the study or progressed to the Extension study by the date of Amendment 3 Protocol approval.

<sup>a</sup> Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration on Day 1.

<sup>b</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature ([Section 8.1.4](#)). On Day 1, vital signs should be collected prior to study drug administration.

<sup>c</sup> If subject comes to the center and/or chooses to be admitted on Day -1.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>f</sup> Must occur within 72 hours prior to dosing.

<sup>g</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>h</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see [Section 8](#)).

<sup>i</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>j</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>k</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>l</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [within 1 min prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 [within 1 min post-infusion], 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose),

Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>m</sup>New adverse events (AEs) and serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit, or until new anticancer therapy is initiated.

**Table 2: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																			<b>End of Part 2</b>
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup>		
Informed consent	X																			
Subject demographics and baseline characteristics	X																			
Medical history and cancer history	X																			
Inclusion/exclusion criteria	X																			
Physical examination	X																		X	
Height (cm)	X																			
Weight (kg)	X																		X	
Body mass index (kg/m <sup>2</sup> )	X																			
Vital signs <sup>c</sup>	X	X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
HBV/HCV/HIV screening <sup>e</sup>	X																			
Clinical laboratory assessments <sup>f</sup>	X <sup>g</sup>																		X	X
Serum pregnancy test (women of childbearing potential)	X																		X <sup>h</sup>	
Electrocardiogram (12-lead) <sup>i</sup>	X		X																X	
ECOG performance status	X																		X <sup>h</sup>	
Confirm diagnosis with CT scan <sup>j</sup>	X																			
Subject confinement		X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
[ <sup>14</sup> C]-niraparib oral administration <sup>k</sup>			X																	

**Table 2: Schedule of Assessments: Part 2 (Continued)**

Assessment or Procedure	Day Relative to First Dose of Study Drug																		
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup>	End of Part 2
Pharmacokinetic blood sampling <sup>l</sup>		X	X	X	X	X	X			X			X					X	X <sup>l</sup>
Blood sample for metabolite profiling <sup>m</sup>		X	X	X	X	X	X			X			X					X	X
Urine collection <sup>n</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Fecal collection <sup>o</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Bone marrow aspirate and biopsy sample collection (whole blood) for cytogenetic analysis <sup>p</sup>																			X
Whole blood samples for cytogenetic analysis <sup>q</sup>	X																		X <sup>r</sup>
Whole blood sample for FISH, MDS	X <sup>s</sup>																		
Prior/concomitant medication and AE monitoring <sup>t</sup>	X	X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X			X	X	

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration on Day 1.

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote <sup>n</sup> and Footnote <sup>o</sup>), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped. Note that only urine/fecal and PK blood collections may extend beyond Day 22; other assessments do not need to be repeated.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature ([Section 8.1.4](#)). On Day 1, vital signs should be collected prior to study drug administration.

<sup>d</sup> If subject comes to the center and/or chooses to be admitted on Day -1.

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>f</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>g</sup> Must occur within 72 hours prior to dosing.

<sup>h</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see [Section 8](#)).

<sup>i</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>j</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>k</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity (3 × 100-mg capsules, labeled active pharmaceutical ingredient [3 x 33.3 µCi of radioactivity]), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<sup>l</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose). Participation in Part 2 of the study may extend beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm$  24 hours of the final urine or fecal sample ([Section 7](#)).

<sup>m</sup> Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>n</sup> Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. See [Section 7.2](#) for collection stop criteria.

<sup>o</sup> Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. See [Section 7.3](#) for collection stop criteria.

<sup>p</sup> For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the local hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria (Vardiman 2009) and other sample testing results related to MDS/AML. Report data will be entered into EDC on the appropriate eCRE pages and the site must keep a copy of all reports with the subject's study file.

<sup>q</sup> Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Laboratory Manual.

<sup>r</sup> Blood sample for cytogenetic analysis only if subject discontinues.

<sup>s</sup> FISH, MDS test result must be negative for cytogenetic abnormalities commonly observed in myeloid malignancies. The FISH, MDS result must be received prior to randomization.

<sup>t</sup> New adverse events (AEs) and serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit, or until new anticancer therapy is initiated.

**Table 3: Schedule of Assessments: Open-Label Extension Study**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c,d</sup>
		Day 1	Day 8	Day 15	Day 22		
Inclusion/exclusion criteria	X						
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>e</sup>	X		X	X	X	X	X
Complete blood count (CBC) <sup>f</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>g</sup>	X			X		X	X
Pregnancy test (women of childbearing potential) <sup>h</sup>	X					X	X
Study drug dispensed/collected <sup>i</sup>		X				X	X
Electrocardiogram (12-lead) <sup>j</sup>		X				X	X
ECOG performance status	X					X	X
Niraparib oral administration (in-house) <sup>k</sup>		X	X	X	X	X	
Bone marrow aspirate and biopsy sample collection (whole blood) for cytogenetic analysis <sup>l</sup>					X		
Whole blood samples for cytogenetic analysis <sup>m</sup>	X						X
Whole blood samples for FISH, MDS	X <sup>n</sup>						

**Table 3: Schedule of Assessments: Open-Label Extension Study (Continued)**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c, d</sup>
		Day 1	Day 8	Day 15	Day 22		
Concomitant medication and AE monitoring <sup>o</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

a Upon completion of Part 1 or 2 of the study (or if subject is non-evaluable for PK in Part 1 or 2), subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit.

b Treatment cycles are 28 ( $\pm 3$ ) days. Visits (except Cycle 1) will continue approximately every 4 weeks until treatment discontinuation

c The EOT visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)). If the subject discontinues due to disease progression, then the CT scan (taken per standard of care) closest to the time of progression (EOT) should be provided.

d New malignancy information will be collected for all subjects via telephone every 90 days following the treatment discontinuation visit (subjects in the extension study only). See [Section 8.1.12](#).

e Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature ([Section 8.1.4](#)). On Day 1, vital signs should be collected prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.

f The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.

g Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.

h A serum pregnancy test will be conducted at the Screening Visit and at EOT. A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4/Day 1, Cycle 7/Day 1, etc.).

i Subjects will take 300 mg (3  $\times$  100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. No fasting period is required during the extension study. No new capsules will be dispensed at EOT.

j Subjects will have a 12-lead ECG at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at EOT.

k Niraparib is self-administered daily, except on study visit days. On days of study visits (eg, Cycle 1, Day 1, 8, 15, and 22; Cycle n, Day 1) subjects should refrain from taking niraparib until after clinical assessments are performed.

<sup>1</sup> For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the local hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria (Vardiman 2009) and other sample testing results related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the subject's study file.

<sup>m</sup> Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Laboratory Manual.

<sup>n</sup> FISH, MDS test result must be negative for cytogenetic abnormalities commonly observed in myeloid malignancies. The FISH, MDS result must be received prior to randomization.

<sup>o</sup> New adverse events (AEs) and serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit, or until new anticancer therapy is initiated.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 4: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
ADP	adenosine diphosphate
AE	adverse event
A <sub>e</sub> (day)	amount of drug excreted in the urine in a 24-hour period
A <sub>e</sub> (total)	total amount of drug excreted in the urine
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AMS	accelerator mass spectrometry
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC <sub>0-inf</sub>	area under the plasma concentration-time curve from time 0 to infinity
AUC <sub>0-last</sub>	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
CA-125	cancer antigen 125
CBC	complete blood count
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent oral clearance
C <sub>max</sub>	maximum observed plasma concentration
CNS	central nervous system
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	cytochrome P450 1A2
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
f	extent of absorption

**Table 4: Abbreviations and Specialist Terms (Continued)**

Abbreviation or Specialist Term	Explanation
GCP	good clinical practice
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	homologous recombination
IB	investigator's brochure
IC <sub>20</sub>	20% maximum inhibitory concentration
IC <sub>50</sub>	50% maximum inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
LC-MS	liquid chromatography-mass spectrometry
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LSC	liquid scintillation counting
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
MS	mass spectrometry
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
P-gp	P-glycoprotein
PARP	poly (adenosine diphosphate-ribose) polymerase
PI	principal investigator
PK	pharmacokinetic
QD	once a day
QTc	corrected QT interval

**Table 4: Abbreviations and Specialist Terms (Continued)**

Abbreviation or Specialist Term	Explanation
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
$T_{max}$	time to reach maximum observed plasma concentration
ULN	upper limit of normal
Vd/F	apparent oral volume of distribution

## 1. INTRODUCTION

### 1.1. Niraparib

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally active poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor with nanomolar potency that is being developed for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway or that are driven by PARP-mediated transcription factors.

#### 1.1.1. DNA Repair, Cancer, and PARP Inhibition

The PARP-1 and -2 enzymes, which are zinc-finger DNA-binding enzymes, play a crucial role in DNA repair. Upon formation of single-strand DNA breaks, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones, various DNA repair proteins, and PARP itself, which results in chromatin relaxation and fast recruitment of DNA repair factors that access and repair DNA breaks.

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of tumor cells than on normal cells. Therefore, a hypothesis is that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways.

Clinical studies have shown that PARP inhibitors have antitumor activity in certain types of cancer (Fong et al, 2009; Audeh et al, 2010; Gelmon et al, 2011; Kummar et al, 2012; Ledermann et al, 2012). Nonclinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with homozygous inactivation of either *BRCA-1* or *BRCA-2*; these breast cancer genes are known to be important in the HR DNA repair pathway. Germline mutations of *BRCA-1* and -2 are found in the majority of subjects with inherited breast or ovarian cancer. Inactivation of *BRCA-1* and -2 by mechanisms other than mutations, including somatic mutations and gene silencing by promoter hypermethylation, occurs in a significant portion of several sporadic cancers. In particular, for ovarian cancer, somatic *BRCA-1* or -2 mutations are found in 10% to 15% of all epithelial ovarian carcinomas, and strongly reduced expression of *BRCA-1* has been observed in a significant portion of sporadic ovarian cancers. Collectively, up to 40% to 60% of ovarian cancers might be responsive to PARP inhibitors as a consequence of defects in the BRCA-HR pathway, indicating a great potential for this approach in the therapy of ovarian cancer.

#### 1.1.2. Niraparib Nonclinical Studies

Niraparib inhibits normal DNA repair mechanisms and induces synthetic lethality when administered to cells with HR defects. In a *BRCA-1* mutant xenograft study in mice, niraparib dosed orally caused tumor regression, which was mirrored by a greater than 90% reduction in

tumor volume compared to control. In a *BRCA-2* mutant xenograft study in mice, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib was evaluated for its potential effects on cardiovascular and neurological function using several experimental safety pharmacology models. Niraparib inhibited the human Ether-à-go-go-related gene (hERG) current with a 50% maximal inhibitory concentration ( $IC_{50}$ ) value of 10  $\mu$ M and a 20% maximal inhibitory concentration ( $IC_{20}$ ) value of 3.8  $\mu$ M. Niraparib was administered intravenously during 3 sequential 30-minute periods at 1, 3, and 10 mg/kg to determine the effect of niraparib on cardiovascular function in 3 anesthetized dogs. Niraparib had no effect on the corrected QT interval (QTc; average plasma concentration  $\leq$ 15.3  $\mu$ M at 10 mg/kg). Mean arterial pressure and heart rate were increased at all doses evaluated, but the QRS cardiac interval was only increased at 10 mg/kg. Niraparib had no effect on neurological function in conscious mice at a single oral dose of 100 mg/kg.

The pharmacokinetics (PK) of niraparib in male Sprague-Dawley rats were determined following intravenous (IV; 3 mg/kg) and oral (5 mg/kg) administration. In male beagle dogs, PK studies were conducted following IV (1 mg/kg) and oral (3 mg/kg) administration. Following IV administration, niraparib demonstrated moderate-to-high clearance (28 and 31 mL/min/kg), a high volume of distribution (6.9 and 12.3 L/kg), and moderate terminal half-lives (3 and 6 hours) in rats and dogs, respectively. The oral bioavailability of niraparib was reasonable in both species (approximately 27% in rats and 57% in dogs).

Niraparib was investigated in 1-month oral toxicity studies in order to support daily dosing of the compound in humans, where niraparib was administered to rats and dogs by oral gavage once a day (QD) for up to 4 weeks followed by an approximately 2-week recovery period. Overall, nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. In the 1-month repeat-dose toxicity study in rats, mortality and physical signs were limited to the high dose (50 mg/kg/day). All changes observed at 50 mg/kg/day were resolved at the end of the 2-week recovery period or demonstrated reversibility, except for minimal treatment-related arterial hypertrophy in the heart and increased trabecula in the bone. At 10 mg/kg/day, there were no treatment-related changes other than increased urine volume in males. Based on these findings, the no observed adverse effect level (NOAEL) in the rat study was 10 mg/kg/day. The dose causing severe irreversible toxicity and death was 50 mg/kg/day. In the dog, decreases in hematology values were observed at a dose of 15 mg/kg/day, and all hematology changes seen during the dosing phase were resolved at the end of the recovery period. Although a decrease in amount of spermatogenic epithelium was observed after 1-month dosing at 6 mg/kg/day and 15 mg/kg/day and was not resolved at the end of the 2-week recovery period, the continued presence of spermatogenic epithelium supports that this change would eventually resolve. Therefore, based on these findings, the NOAEL for the dog study was 3 mg/kg/day.

The niraparib nonclinical studies are described in detail in the [Investigator's Brochure \(IB\)](#).

### **1.1.3. Niraparib Clinical Studies**

The niraparib clinical studies are described in detail in the [IB](#).

### **1.1.3.1. Phase 1 Studies**

Niraparib has been evaluated in a series of Phase 1 clinical studies in subjects with solid tumors. For these studies, niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide. Treatment with niraparib has been generally well-tolerated. Refer to the Investigator's Brochure for more information.

The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were fatigue, nausea, anemia, constipation, thrombocytopenia, vomiting, decreased appetite, neutropenia, headache, diarrhea, dyspnea, cough, leukopenia, hyponatremia, back pain, hyperglycemia, insomnia, abdominal pain, hypokalemia, blood alkaline phosphatase increased, pain in extremity, hypertension, peripheral edema, rash, dizziness, electrocardiogram (ECG) QT prolonged, pyrexia, abdominal distension, urinary tract infection, weight decreased, abdominal pain lower, alopecia, neoplasm malignant, dry mouth, hypoalbuminemia, musculoskeletal pain, stomatitis, arthralgia, blood creatinine increase, chills, dyspepsia, hypomagnesemia, paresthesia, aspartate aminotransferase increased, dehydration, musculoskeletal chest pain, neck pain, alanine aminotransferase (ALT) increased, dysgeusia, myalgia, and palpitations.

The most commonly reported drug-related (>5.0%) AEs (all grades) in the clinic were: fatigue, nausea, anemia, thrombocytopenia, decreased appetite, neutropenia, vomiting, constipation, leukopenia, diarrhea, insomnia, dyspnea, ECG QT prolonged, headache, stomatitis, hyponatremia, and alopecia.

### **1.1.3.2. Phase 3 Studies**

The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline *BRCA* mutation breast cancer subjects ([PR-30-5010-C](#); BRAVO) and to platinum-sensitive ovarian cancer subjects ([PR-30-5011-C](#); NOVA). Treatment with niraparib has been generally well tolerated. Refer to the Investigator's Brochure for more information.

### **1.1.4. Risks and Benefits**

The potential benefit of niraparib treatment for patients with cancer is tumor regression.

Nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation ([Section 1.1.3.1](#)). The Investigator should monitor subjects closely for these AEs.

As Phase 1 studies have shown that niraparib is safe and well tolerated, the potential benefits outweigh the potential risks.

When taking niraparib, caution should be used when also taking medications that are inducers of cytochrome P450 1A2 (CYP1A2) or inhibitors or inducers of P-glycoprotein (P-gp; [Section 5.2](#)). The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs ([Section 5.2](#)).

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib.

Guidance on monitoring subjects for new events of MDS/AML and the follow-up of subjects with suspected MDS/AML is provided in [Section 3.4](#) and [Section 8.1.8](#).

## **1.2. Rationale for Current Study**

This is an open-label study with 2 parts, plus an extension study following completion of Parts 1 or 2, that is being conducted in approximately 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) with cancer to examine the absorption, metabolism, excretion, and absolute bioavailability of niraparib. This study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

The oral bioavailability of niraparib has been determined in rats and dogs ([Section 1.1.2](#)), but has yet to be determined in human subjects, including those with cancer. Therefore, this study will examine the absolute oral bioavailability of niraparib and the absorption, metabolism, excretion, and mass balance of oral [ $^{14}\text{C}$ ]-niraparib in subjects with cancer.

The oral dose of niraparib used in this study is 300 mg, which is the maximum tolerated dose of niraparib. A total of 144 subjects have been treated with niraparib up to 400 mg QD PO in Phase 1 studies, and the 300-mg daily dose of niraparib is considered safe and generally well tolerated ([IB](#)). The 300-mg daily dose of niraparib is currently being administered in 2 Phase 3 studies ([Section 1.1.3.2](#)).

This study will be the first-in-human administration of the IV formulation of niraparib. Data from the nonclinical studies did not demonstrate any safety issues that would preclude testing of IV niraparib in humans, and a microdose (100  $\mu\text{g}$ ) of niraparib is being administered in the current study.

## **2. STUDY OBJECTIVES AND PURPOSE**

### **2.1. Primary Objective**

- To determine the absolute bioavailability of niraparib by using an IV niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer.

### **2.2. Secondary Objectives**

- To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer.
- To evaluate the safety and tolerability of niraparib in subjects with cancer.

### 3. INVESTIGATIONAL PLAN

#### 3.1. Overall Study Design

This is an open-label study with 2 parts, plus an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP).

**Part 1:** The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center on Day 1 at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of  $100 \mu\text{g}$  niraparib, containing approximately  $1 \mu\text{Ci}$  of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center on Day 1 at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately  $100 \mu\text{Ci}$  of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu\text{Ci}$  of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. Participation may continue beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm 24$  hours of the final urine or fecal sample ([Section 7.2](#) and [Section 7.3](#)).

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments. No fasting period is required during the extension study. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject ([Section 3.4](#)). Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

The schedule of assessments for Part 1, Part 2, and the extension study are presented in [Table 1](#), [Table 2](#), and [Table 3](#), respectively.

### 3.2. Number of Subjects

There will be 6 subjects in Part 1 of the study and 6 subjects in Part 2 of the study. Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

### 3.3. Treatment Assignment

At the Screening Visit, subjects will be offered the option to participate in either Part 1 or Part 2 of the study until 1 part of the study is fully enrolled, at which time subjects can only be screened for the remaining part of the study, or for future replacements ([Section 4.4.1](#)). Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

### 3.4. Dose Adjustment Criteria

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject. Treatment must be interrupted for any nonhematologic National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.02; HHS 2009) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days of dose interruption, at the Investigator's discretion the subject may restart treatment with niraparib, but with a dose level reduction according to [Table 5](#) if prophylaxis is not considered feasible. Upon re-challenge, if the event recurs at a similar or worse grade, then treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted.

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 28-day dose interruption period, and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

**Table 5: Niraparib Dose Reductions for Nonhematologic Toxicities**

Event <sup>a</sup>	Dose <sup>b</sup>
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE $\geq$ 28 days	Discontinue study drug

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; QD, once a day; SAE, serious adverse event.

<sup>a</sup> Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject.

<sup>b</sup> Dose not to be decreased below 100 mg QD.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts, as outlined in [Table 6](#).

**Table 6: Niraparib Dose Modification/Reduction for Hematologic Toxicities**

Event	Dose Modification
Platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at the same dose or a reduced dose based on clinical judgment.
Second occurrence of platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count $< 75,000/\mu\text{L}^a$	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophils $< 1000/\mu\text{L}$	Study drugs must be interrupted until neutrophil counts are $\geq 1500/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin $\leq 8 \text{ g/dL}$	Study drugs must be interrupted until hemoglobin is $\geq 9 \text{ g/dL}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviation: CBC, complete blood count.

<sup>a</sup> For subjects with a platelet count  $\leq 10,000/\mu\text{L}$ , a prophylactic platelet transfusion per guidelines may be considered (Schiffer et al., 2001; Slichter, 2007). For subjects taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as  $\leq 20,000/\mu\text{L}$

If dose interruption or modification is required at any point during the study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for CBC will be required for an additional 28 days after the AE has been resolved to the specified levels, after which monitoring every 28 days may resume. Weekly blood draws for CBC can be collected either at the study center or local laboratories. If the hematologic toxicity has not recovered to the specified levels within 28 days of the dose interruption period and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

Any subject requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed.

The subject must be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, then the subject must permanently discontinue study treatment.

For major surgery while on treatment, up to 28 days of drug interruption is allowed.

Once the dose of study drug has been reduced, any re-escalation must be discussed with the Medical Monitor.

All dose interruptions and reductions (including any missed doses) and the reasons for the interruptions and reductions will be recorded in the electronic case report form (eCRF).

### **3.5. Criteria for Study Termination**

If in the opinion of the Investigator or Sponsor there is reasonable or sufficient cause, this study may be prematurely terminated at any time. Written notification documenting the reason for study termination will be provided to the Investigator or Sponsor by the terminating party.

Circumstances that may warrant termination include study center performance issues, a potential new finding with the study drug, or changes in the development program. See [Section 4.4](#) for subject withdrawal criteria. Additional circumstances include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enroll subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of study drug

Should the study be stopped prematurely, all study materials must be returned to the Sponsor or be disposed of according to the Sponsor's specifications.

## 4. SELECTION AND WITHDRAWAL OF SUBJECTS

### 4.1. Subject Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has a histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy or have progressed despite standard therapy; or has refused standard therapy (or for which no standard therapy exists); and subject may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - Platelets  $\geq 150,000/\mu\text{L}$
  - Hemoglobin  $\geq 9 \text{ g/dL (5.6 mM)}$
  - Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 4.3](#)).
8. Subject is able to take oral medications.
9. Subject must agree to blood samples during screening and at the end of treatment for cytogenetic analysis

### 4.2. Subject Exclusion Criteria

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing >20% of the bone marrow.
2. Subject has persistent >Grade 2 toxicity from prior cancer therapy.
3. Subjects must not have any known, persistent (>4 weeks) ≥Grade 3 hematological toxicity or fatigue from prior cancer therapy.
4. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
5. Subject has known hypersensitivity to the components of niraparib.
6. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
7. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
8. Subject received (or is anticipated to receive) a platelet transfusion within 4 weeks of study drug administration.
9. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study, interfere with the subject’s participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
10. Subject has any known history of MDS or a pre-treatment cytogenetic testing result at risk for a diagnosis of MDS/AML.
11. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
12. Subject is immunocompromised with an active event and is being treated with medications.
13. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
14. Subject has a corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.

15. Subject is receiving concomitant medications that prolong QTc and is unable to discontinue use for the duration of the study ([Appendix 16.1](#)).
16. Subject is starting chemotherapy within 3 weeks of study drug administration.
17. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
18. Subject has a history of illicit drug use.
19. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
20. Subject is currently participating in another clinical study and has received an investigational drug, or has participated in a clinical study and has received an investigational drug within 21 days of study drug administration.
21. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months prior to study drug administration (for subjects participating in Part 1) or within 30 days prior to study drug administration (for subjects participating in Part 2).

#### **4.3. Restrictions During Study**

Restrictions during the study include the following:

1. If sexually active, subjects of reproductive potential and their partners must agree to the use of 2 of the following highly effective forms of contraception throughout their participation in the study and for 90 days after the last dose of study drug:
  - Condom with spermicide and one of the following:
    - Oral contraceptive or hormonal therapy (eg, hormone implants)
    - Placement of an intrauterine device

Acceptable nonhormonal birth control methods include the following:

- Total sexual abstinence
- Vasectomized sexual partner and use of a male condom, with subject assurance that partner received postvasectomy confirmation of azoospermia
- Tubal occlusion and use of a male condom with spermicide
- Intrauterine device and use of a male condom with spermicide

Acceptable hormonal birth control methods with use of a male condom with spermicide include the following:

- Etonogestrel implants (eg, Implanon®, Norplant®)
- Normal and low dose combined oral contraceptive pills
- Norelgestromin/ethynodiol transdermal system

- Intravaginal device (eg, ethinyl estradiol and etonogestrel)
  - Cerazette® (desogestrel), which is currently the only highly efficacious progesterone-based pill
2. No other anticancer therapy is permitted during the course of study treatment for any subject. If the subject discontinues study drug, this restriction no longer applies. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.
  3. Prophylactic cytokine (granulocyte colony-stimulating factor) administration should not be given in the first cycle of the extension study but may be administered in subsequent cycles according to local guidelines.
  4. An increased risk of infection with the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown, so live virus and bacterial vaccines should not be administered to subjects in the study.
  5. Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to receiving study drug and/or within 6 hours after receiving study drug.
  6. Subjects who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.
  7. Blood transfusions within the first 3 days post study drug administration are permissible if the blood transfusion is <500 mL/day.
  8. Subjects are not to take medications known to prolong QTc ([Section 16.1](#)) while participating in the study.

#### **4.4. Subject Withdrawal Criteria**

A subject may be discontinued from treatment or from the study for the following reasons:

- AE
  - For the extension study only, a treatment-related CTCAE Grade 3 or 4 AE that has not reverted to CTCAE Grade 1 or less within 28 days of dose interruption. At the Investigator's discretion, following dose interruption (no longer than 28 days), subjects may be considered for dose reductions ([Section 3.4](#)), providing they have not already undergone the maximum number of 2 dose reductions allowed. If a CTCAE Grade 3 or 4 AE recurs upon re-challenging with study drug at the lowest allowable dose, the subject must permanently discontinue treatment.
- Unacceptable toxicity
  - For the extension study only, if the subject experiences a dose interruption or modification because of a hematologic toxicity and the platelet count has not reverted to  $\geq 100,000/\mu\text{L}$  within 28 days of dose interruption, the subject should be discontinued.

- Severe noncompliance with the protocol, as judged by the Investigator and/or Sponsor.
- Subject becomes pregnant
- It is in the best interest of the subject, as judged by the Investigator and/or Sponsor
- Subject withdraws consent
- Sponsor decision to terminate study
- For the extension study only, disease progression and/or clinical criteria per standard of care

Subjects who discontinue from treatment will continue to receive follow-up safety assessments (see [Section 8](#)) as part of the study for 30 days from the last dose, unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the subject, who is at any time and for any reason free to discontinue their participation in the study, without prejudice to further treatment
- Death
- Loss to follow-up

If a subject is lost to follow-up or withdraws from study treatment, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.

#### **4.4.1. Replacement of Subjects**

After consultation between the Sponsor and the Principal Investigator (PI), enrollment may be extended to replace subject(s) discontinued during the study. Replacement subjects will be assigned the next available dosing number for the part of study in which the discontinued subjects were enrolled.

## 5. TREATMENT OF SUBJECTS

### 5.1. Description of Study Drug

The investigational products that will be used in this study are summarized in Table 7.

**Table 7: Investigational Product**

Investigational Product			
<b>Product Name</b>	niraparib	[ <sup>14</sup> C]-niraparib IV solution	[ <sup>14</sup> C]-niraparib
<b>Dosage Form</b>	100-mg capsules	sterile solution for IV administration	capsules
<b>Unit Dose</b>	300 mg (3 × 100-mg capsules)	100 µg (1 µCi total radioactivity)	300 mg (3 × 100-mg capsules, 3 x 33.3 µCi of radioactivity [100 µCi total radioactivity])
<b>Route of Administration</b>	oral	IV	oral
<b>Study Phase Taken</b>	Part 1 and Extension	Part 1	Part 2

Abbreviation: IV, intravenous.

### 5.2. Prior and Concomitant Medications

Any medication the subject takes during the study other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication.

All prior and concomitant medications will be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Known prior medications that exclude a subject from participating in the study are described in the Exclusion Criteria ([Section 4.2](#)). Prohibited concomitant medications are described in [Section 4.3](#). Additionally, niraparib has potential to induce CYP1A2. Therefore, subjects should be advised to use caution when taking medications that are also inducers of CYP1A2. Examples of CYP1A2 inducers include montelukast, phenytoin, moricizine, omeprazole, and phenobarbital ([HHS 2012](#)). Niraparib is a substrate for P-gp; therefore, subjects should be advised to use caution when taking medications that are inhibitors or inducers of P-gp. Examples of P-gp inhibitors include the following ([HHS 2012](#)): amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil. Examples of P-gp inducers include the following ([HHS 2012](#)): avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir-ritonavir. Permitted anti-nausea medications are dexamethasone, aprepitant, and granisetron.

Subjects must not be receiving medications that prolong QTc at Screening and for the duration of the study ([Section 16.1](#))

The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs.

### **5.3. Treatment Compliance**

The study staff will maintain an ongoing record of the dispensing and administration of study drug for each subject. For the extension study, subjects will be instructed to return any unused study drug to the study center during their visit on the first day of each cycle or at EOT. Drug accountability will be performed on capsules dispensed versus returned to the study center at each visit and the number of days since the last visit.

### **5.4. Randomization and Blinding**

Subjects will not be randomly assigned and instead may choose in which part of the study to participate ([Section 3.3](#)). This is an unblinded study.

## **6. STUDY DRUG MATERIALS AND MANAGEMENT**

### **6.1. Study Drug**

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor.

### **6.2. Study Drug Packaging and Labeling**

Niraparib 100-mg capsules (unlabeled active pharmaceutical ingredient) will be packed in high-density polyethylene bottles with child-resistant closures. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-subject-specific.

For the extension study, each dosing container will contain a sufficient number of capsules for 1 treatment cycle. Niraparib will be dispensed to subjects on Day 1 of every cycle of the extension study.

The IV solution and oral capsules will be prepared for dosing by Quotient Clinical from [<sup>14</sup>C]-niraparib active pharmaceutical ingredient following Good Manufacturing Practices. Information on the preparation, packaging, and labeling of the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity per 300-mg dose) of niraparib can be found in the investigational medicinal product dossier.

### **6.3. Study Drug Storage**

All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed to the subjects, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

Information for storing the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity) of niraparib can be found in the investigational medicinal product dossier.

### **6.4. Study Drug Administration**

For Part 1, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For Part 2, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3\text{ }\mu\text{Ci}$  of radioactivity]), on Day 1 after an overnight fast of at least 10 hours.

Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For the extension study, 300 mg of niraparib ( $3 \times 100\text{-mg}$  capsules, unlabeled active pharmaceutical ingredient) will be administered orally QD until the subject meets 1 of the withdrawal criteria ([Section 4.4](#)); dose interruptions and reductions will be allowed based on treatment side effects ([Section 3.4](#)). No fasting period is required during the extension study. Subjects will be instructed to take the niraparib dose at the same time of day, preferably in the morning. The first dose will be administered at the study center. Subjects must swallow and not chew the capsules, and the consumption of water is permissible. On days of study visits (eg, Cycle 1, Day 1, 8, 15, and 22; Cycle n, Day 1), subjects should refrain from taking niraparib until after clinical assessments are performed.

## **6.5. Study Drug Accountability**

The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes the subject number, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as “returned” and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. When the study monitor visits the site, he or she will reconcile the drug accountability log with the products stored in the pharmacy.

## **6.6. Study Drug Handling and Disposal**

After receiving Sponsor approval in writing, the study center is responsible for returning all unused or partially used study drug to Sponsor or a designated third party or for preparing the study drug for destruction at the investigational study center.

## 7. PHARMACOKINETIC ASSESSMENTS

Subjects will undergo the following procedures according to the schedule of assessments presented in [Table 1](#), [Table 2](#), and [Table 3](#).

### 7.1. Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling

For Part 1, blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [within 1 min prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 [within 1 min post-infusion], 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For Part 2, blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose). Participation in Part 2 of the study may extend beyond Day 22 based on the amount of radioactivity recovered. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm 24$  hours of the final urine or fecal sample. ([Section 7.2](#) and [Section 7.3](#)).

For Part 2, blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

The exact time that each sample is collected will be recorded by the study center, regardless of whether the sample is collected within the specified windows. A detailed description of the blood sample schedule and aliquot collection is included in [Table 8](#) and [Table 9](#) for Parts 1 and 2, respectively. Blood samples that will be used to measure the plasma concentration of [ $^{14}\text{C}$ ]-niraparib with accelerator mass spectrometry (AMS) in Part 1 will be transferred for analysis. Refer to the laboratory manual for further details on sample handling and shipping.

**Table 8: Part 1 Blood Sample Schedule and Aliquot Collection**

Day From Oral Dose	Time From Oral Dose	Time From Start of IV Infusion (hour)	Blood Samples for AMS Plasma Analysis of IV Dose (mL) <sup>a</sup>	Blood Samples for LC-MS/MS Plasma Analysis of Oral Dose (mL) <sup>b</sup>	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	—	2	2	8
	1 hr [ $\pm 2$ min]	—	—	2	4
	1.5 hr [ $\pm 2$ min]	—	—	2	4
	2 hr [within 1 min prior to IV infusion]	0 <sup>c</sup>	2	2	8
	2.125 hr [ $\pm 1$ min] <sup>d</sup>	0.125 <sup>c</sup>	2	—	4
	2.25 hr [within 1 min post-infusion] <sup>e</sup>	0.25 <sup>c</sup>	2	—	4
	2.33 hr [ $\pm 1$ min] <sup>f</sup>	0.33 <sup>c</sup>	2	—	4
	2.66 hr [ $\pm 1$ min] <sup>g</sup>	0.66 <sup>c</sup>	2	—	4
	3 hr [ $\pm 2$ min]	1 <sup>c</sup>	2	2	8
	4 hr [ $\pm 5$ min]	2 <sup>c</sup>	2	2	8
	6 hr [ $\pm 5$ min]	4 <sup>c</sup>	2	2	8
	12 hr [ $\pm 15$ min]	10 <sup>c</sup>	2	2	8
2	24 hr [ $\pm 1$ hr]	22 [ $\pm 1$ ]	2	2	8
3	48 hr [ $\pm 2$ hr]	46 [ $\pm 2$ ]	2	2	8
4	72 hr [ $\pm 4$ hr]	70 [ $\pm 4$ ]	2	2	8
5	96 hr [ $\pm 4$ hr]	94 [ $\pm 4$ ]	2	2	8
7	144 hr [ $\pm 4$ hr]	142 [ $\pm 4$ ]	2	2	8
9	192 hr [ $\pm 8$ hr]	190 [ $\pm 8$ ]	2	2	8
11	240 hr [ $\pm 12$ hr]	238 [ $\pm 12$ ]	2	2	8
13	288 hr [ $\pm 12$ hr]	286 [ $\pm 12$ ]	2	2	8
15	336 hr [ $\pm 12$ hr]	334 [ $\pm 12$ ]	2	2	8
22	504 hr [ $\pm 12$ hr]	502 [ $\pm 12$ ]	2	2	8

Abbreviations: AMS, accelerator mass spectrometry; IV, intravenous; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

<sup>a</sup> These samples will include 1 sample for AMS analysis (2 mL), and 1 sample that will be used as either a back-up sample for AMS analysis or potentially for LC-MS/MS analysis (2 mL).

<sup>b</sup> These samples will include 1 sample for LC-MS/MS analysis (2 mL) and 1 back-up sample (2 mL).

<sup>c</sup> Refer to Time From Oral Dose column for collection windows for the 0-10 hr Time From Start of IV Infusion.

<sup>d</sup> 2 hr 7.5 min

<sup>e</sup> 2 hr 15 min

<sup>f</sup> 2 hr 20 min

<sup>g</sup> 2 hr 40 min

**Table 9: Part 2 Blood Sample Schedule and Aliquot Collection**

Day	Time From Oral Dose	Blood Samples for LC-MS/MS Plasma Analysis <sup>a</sup> (mL)	Blood Sample for LSC Plasma Analysis (mL)	Blood Sample for LSC Whole Blood Analysis (mL)	Metabolite Profiling LC-MS/LC-MS/MS (mL)	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	2	2	2	2	10
	1 hr [ $\pm 2$ min]	2	2	2	2	10
	1.5 hr [ $\pm 2$ min]	2	2	2	—	8
	2 hr [ $\pm 2$ min]	2	2	2	2	10
	3 hr [ $\pm 2$ min]	2	2	2	2	10
	4 hr [ $\pm 5$ min]	2	2	2	—	8
	6 hr [ $\pm 5$ min]	2	2	2	2	10
	12 hr [ $\pm 15$ min]	2	2	2	2	10
2	24 hr [ $\pm 1$ hr]	2	2	2	2	10
3	48 hr [ $\pm 2$ hr]	2	2	2	2	10
4	72 hr [ $\pm 4$ hr]	2	2	2	2	10
5	96 hr [ $\pm 4$ hr]	2	2	2	2	10
6	120 hr [ $\pm 4$ hr]	2	2	2	2	10
8	168 hr [ $\pm 4$ hr]	2	2	2	2	10
11	240 hr [ $\pm 12$ hr]	2	2	2	2	10
15	336 hr [ $\pm 12$ hr]	2	2	2	2	10
22	504 hr [ $\pm 12$ hr]	2	2	2	2	10

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> These samples will include 1 sample for analysis (2 mL), and 1 back-up sample (2 mL).

## 7.2. Urine Sample Collection

Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be

quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. The discontinuation of urine sample collections will be based on:

1. If the total radioactivity in the Day 14 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then urine samples will be collected every 24 hours through Day 21.
2. If the total radioactivity in the Day 21 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then urine samples will continue to be collected every 24 hours.
3. Urine sample collection will stop at the end of Day 21 if the recovered radioactivity is  $<1\%$  (per 24 hours) for the 2 consecutive days prior to Day 21 (Days 19 and 20). If this is not the case, then collection will stop as soon as the recovered radioactivity is  $<1\%$  (per 24 hours) for 2 consecutive days after Day 21.

A detailed description of the urine sample schedule and the aliquot collection is included in Table 10. Refer to the laboratory manual for further details on sample storage conditions.

**Table 10: Urine Sample Schedule and Aliquot Collection**

Day	Interval (hour)	Niraparib Concentration LC-MS/MS Analysis (mL)	Radioactivity LSC Analysis (mL)	Metabolite Profiling LC-MS /LC-MS/MS (mL)	Total Urine Sample Volume (mL)
1	0 (predose)	$2 \times 3$	1	$3 \times 10$	37
	0-12				
	12-24				
2	24-36				
	36-48				
3	48-72				
4	72-96				
5	96-120				
6	120-144				
7	144-168				
8	168-192				
9	192-216				
10	216-240				
11	240-264				
12	264-288				
13	288-312				

**Table 10: Urine Sample Schedule and Aliquot Collection (Continued)**

Day	Interval (hour)	Niraparib Concentration LC-MS/MS Analysis (mL)	Radioactivity LSC Analysis (mL)	Metabolite Profiling LC-MS /LC-MS/MS (mL)	Total Urine Sample Volume (mL)
14	312-336				
15 <sup>a</sup>	336-360				

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> See above for collection stop criteria.

### 7.3. Fecal Sample Collection

Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. The discontinuation of fecal sample collections will be based on:

1. If the total radioactivity in the Day 14 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then fecal samples will be collected every 24 hours through Day 21.
2. If the total radioactivity in the Day 21 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity is  $\leq 85\%$  (feces and urine), then fecal samples will continue to be collected every 24 hours.
3. Feces sample collection will stop at the end of day Day 21 if the recovered radioactivity is  $<1\%$  (per 24 hours) for the 2 consecutive days prior to Day 21 (Days 19 and 20). If this is not the case, then collection will stop as soon as the recovered radioactivity is  $<1\%$  (per 24 hours) for 2 consecutive days after Day 21.

A detailed description of the fecal sample schedule and the aliquot collection is included in Table 11. Refer to the laboratory manual for further details on sample storage conditions.

**Table 11: Fecal Sample Schedule and Aliquot Collection**

Day	Time (hour)	Aliquot Collection
1	0 (predose)	Fecal samples will be processed per stool and analyzed in 24-hour intervals.
	0-24	
2	24-48	
3	48-72	
4	72-96	
5	96-120	
6	120-144	

**Table 11: Fecal Sample Schedule and Aliquot Collection (Continued)**

Day	Time (hour)	Aliquot Collection
7	144-168	
8	168-192	
9	192-216	
10	216-240	
11	240-264	
12	264-288	
13	288-312	
14	312-336	
15 <sup>a</sup>	336-360	

Abbreviation: LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> See above for collection stop criteria.

## 7.4. Sample Analysis

Analysis of blood, urine, and fecal samples includes the following:

- **Blood:** Blood samples will be analyzed for the plasma concentrations of niraparib and the major metabolite (M1) using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Part 1 blood samples will be analyzed for the plasma concentration of [<sup>14</sup>C]-niraparib using AMS. Part 2 blood samples will be analyzed for the whole blood and plasma concentrations of [<sup>14</sup>C]-niraparib using liquid scintillation counting (LSC). Part 2 plasma blood samples will be analyzed for metabolite profiling and identification using high resolution liquid chromatography-mass spectrometry (LC-MS), in combination with LC-MS/MS (including ion trap instruments). A quantitative LC-MS/MS method will be established for niraparib and the major carboxylic acid metabolite.
- **Urine:** Radioactivity content in urine samples will be determined by LSC. The concentration of niraparib and the major metabolite (M1) will be determined with LC-MS/MS. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).
- **Fecal:** Radioactivity content in fecal samples will be determined by LSC. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).

Pharmacokinetic parameters of interest include the following:

- **Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters: C<sub>max</sub>; time to reach C<sub>max</sub> (T<sub>max</sub>); and AUC from time 0 to the last quantifiable concentration (AUC<sub>0-last</sub>); and if the data allow: AUC from time 0 to infinity (AUC<sub>0-inf</sub>); apparent oral volume of distribution (Vd/F); apparent oral

clearance (CL/F); and half-life ( $t_{1/2}$ ). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

- **Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ ,  $Vd/F$ ,  $CL/F$ , and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$  (day), and total amount of drug excreted in the urine,  $A_e$  (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption ( $f$ ), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.

## 8. ASSESSMENT OF SAFETY

Subjects will undergo the following procedures according to the schedule of assessments presented in [Table 1](#), [Table 2](#), and [Table 3](#).

### 8.1. Safety Parameters

#### 8.1.1. Demographic and Baseline Characteristics

The following demographic information will be documented during the Screening Visit for Parts 1 and 2:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (Asian, Black, Caucasian, Other, Unknown)

The following baseline characteristics will be documented during the Screening Visit for Parts 1 and 2:

- History of drug, alcohol, or other substance abuse
- History of psychiatric illness
- Smoking history

#### 8.1.2. Medical History and Cancer History

Major medical history will be collected during the Screening Visit for Parts 1 and 2. Medical history will be obtained by interviewing the subjects or by reviewing their medical records.

Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis. CT scans should be performed per standard of care. If the subject discontinues due to disease progression, then the CT scan closest to the time of progression (EOT) should also be provided.

The following will be documented for cancer history:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Tumor grade
- Date of start of first treatment
- Agents used in first treatment
- Date of last dose of first treatment
- Date of relapse for each treatment

### **8.1.3. Prior and Concomitant Medications**

For prior medications, subjects will be asked during the Screening Visit for Parts 1 and 2 what medications they have taken during the last 30 days. All concomitant medications will be recorded from the time the subject signs the informed consent form (ICF) through completion of the study.

### **8.1.4. Vital Signs**

Blood pressure, pulse rate, and aural (tympanic) temperature will be measured while the subject is in the supine position at every visit that the subject is at the study center (see [Table 1](#), [Table 2](#), and [Table 3](#) for time points) after the subject has been resting for approximately 2 minutes. Vital signs will be collected prior to study drug administration on Day 1.

### **8.1.5. Weight, Height, and Body Mass Index**

Height (cm) and weight (kg) will be measured without shoes during the Screening Visit for Parts 1 and 2, and body mass index ( $\text{kg}/\text{m}^2$ ) will be calculated. For Parts 1 and 2, weight will also be measured at the Day 22 Visit. For the extension study, weight will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

### **8.1.6. Physical Examination**

The physical examination includes an assessment of general appearance and a review of body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems).

For Parts 1 and 2, the physical examination will be performed at the Screening Visit and at the Day 22 Visit. For the extension study, the physical examination will be performed at the Cycle 1/Day 1 Visit, Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

### **8.1.7. Electrocardiogram**

For Parts 1 and 2, the 12-lead ECG will be performed during the Screening Visit, the Day 1 Visit (predose and 2 hours postdose), the Day 22 Visit, and at EOT. For the Extension Study, the 12-lead ECG will be performed at Cycle 1 Day 1, at the Day 1 Visit (predose and 2 hours postdose) for each cycle during the extension study, and at EOT. Subjects will be in the supine position and resting for approximately 2 minutes before ECGs are recorded. For the measurement of QTc prolongation at the Screening Visit, results will include a mean of triplicate ECG readings (3 readings in rapid succession not more than 2 minutes apart).

### **8.1.8. Clinical Laboratory Assessments**

Laboratory assessments will be performed by the local laboratory at the study center. Blood samples should be drawn prior to study drug administration.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the study center. The Investigator or designee will indicate whether or not the value is of clinical significance and whether or not the subject requires intervention or further monitoring. Clinical significance will be defined as that requiring medical intervention. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality is found in the samples taken during the study, it should be recorded as an AE, and the subject will be followed until the test has normalized or stabilized.

For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization (WHO) criteria (Vardiman 2009) and other sample testing reports related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the subject's study file.

#### **8.1.8.1. Parts 1 and 2 Laboratory Assessments**

Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio.

Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

Assessments will be conducted at the Screening Visit (must be collected within 72 hours prior to dosing), Day 15, and the Day 22 Visit.

For the hematology assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **8.1.8.2. Extension Study Laboratory Assessments**

The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. The CBC will be conducted at the Screening Visit (drawn within 72 hours prior to study drug administration), Days 8, 15, and 22 of Cycle 1; Day 1 of every new cycle; and EOT.

Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. These assessments will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and EOT.

For the CBC, 3 mL of blood will be collected. For the coagulation assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **8.1.9. Laboratory Screenings**

#### **8.1.9.1. Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Screening**

Testing for HBV, HCV, and HIV will only be performed during the Screening Visit for Parts 1 and 2 if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

#### **8.1.9.2. Pregnancy Screen**

A serum pregnancy test will be performed for women of childbearing potential according to standard local procedures during the Screening Visit for Parts 1 and 2. All subjects who do not continue to the extension study will have a serum pregnancy test prior to study exit. Subjects who continue to the extension study will have a serum pregnancy test at the screening visit and at treatment discontinuation for the extension study. A urine pregnancy test will be performed every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.).

### **8.1.10. Eastern Cooperative Oncology Group Performance Scale**

The ECOG performance scale assesses the subject's general well-being and activities of daily life ([Appendix 16.2](#)). To be eligible for enrollment into this study, subjects must have an ECOG performance status of 0 to 2 during the Screening Visit for Parts 1 and 2. ECOG assessments will be conducted at the Parts 1 and 2/Day 22 Visit for subjects who are not enrolling in the extension study. The ECOG performance status will be reassessed during the extension study at the Screening Visit, the Day 1 Visit for Cycle 2 and each subsequent cycle, and at EOT. The same observer should assess performance status each time.

### **8.1.11. Blood and Tissue Samples**

Whole blood samples will be collected for all subjects during screening and at EOT. Some samples will be used to determine eligibility per MDS/AML-related criteria (see [Section 4](#)). These test results must be received prior to randomization. For all eligible subjects, remaining samples will be stored. Stored samples will be evaluated for mutations of selected myeloid-

associated genes if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). Details on blood and tissue sample collection can be found in the Laboratory Manual.

### **8.1.12. New Malignancies**

Although overall survival is not an endpoint in this study, to monitor for MDS/AML and the occurrence of new malignancies, new malignancy information will be collected for all subjects via telephone every 90 days following the treatment discontinuation visit (subjects in the extension study only).

## **8.2. Adverse and Serious Adverse Events**

### **8.2.1. Definition of Adverse Events**

#### **8.2.1.1. Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be documented.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study treatment has been administered.

#### **8.2.1.2. Disease Progression**

The event of disease progression is an efficacy criterion and is therefore not considered an AE. If AEs/SAEs occur in relation to disease progression, then the AEs/SAEs must be reported per AE/SAE reporting requirements described in [Section 8.6](#).

#### **8.2.1.3. Serious Adverse Event**

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:

- Results in death

- Is life-threatening
  - This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability or incapacity
  - Is a congenital anomaly or birth defect
  - Is an important medical event(s)
- An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, disease progression, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

A distinction should be drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

#### **8.2.1.4. Submission of Expedited Reports to Regulatory Authority, Sites, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

Per regulatory requirements, if an SAE report is required to be submitted to a Regulatory Authority a copy of this report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigators/site. TESARO or its designee will submit a copy of the report to their respective IRB or IEC.

### **8.3. Relationship to Study Drug**

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- **Related:** A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by

- concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.
- Likely related: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.
  - Unlikely to be related: A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.
  - Unrelated: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

#### **8.4. Recording Adverse Events**

AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New AEs and SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see [Table 1](#), [Table 2](#), and [Table 3](#) for schedules of events) or until new anticancer therapy is initiated. All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center.

Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the above SAE reporting process.

Abnormal laboratory values that constitute an AE or SAE must be collected. Investigators should assess the severity of AEs according to CTCAE ([HHS 2009](#)).

In general, CTCAE version 4.02 severity grades are the following:

- Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under [Section 8.2.1.2](#). An AE of severe intensity may not be considered serious.

## 8.5. Reports of Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report notification form and reported to the Sponsor.

Pregnancies occurring in subjects enrolled in a study or in a female partner of a male subject must be reported and followed to outcome. The Investigator is responsible for documenting the course and outcome of any pregnancy that occurs while a subject is enrolled in the study and any pregnancy that occurs within 90 days after a subject's last dose.

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions.

Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see [Section 8.6](#)).

The investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The Investigator should follow-up with the subject or the subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs after the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor, or designee, within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs.

## PREGNANCY CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

### 8.6. Reporting Adverse Events

The Investigator must report any SAE within 24 hours of becoming aware of the event. SAEs must be reported using the following contact information:

## SAE REPORTING CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report Form must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the subject's personal identifiers (eg, subject name, medical record number) removed according to local regulations. The Investigator must sign and date all SAE forms.

*The minimum information required for an initial SAE report is:*

- Name of person sending the report (ie, name, address of Investigator)
- Subject identification (screening/randomization number, initials, NOT subject name)
- Protocol number
- Description of SAE
- Causality assessment

In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be

recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information.

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## **9. STATISTICS**

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined in this section. Any deviations from the planned analyses will be described in the final integrated clinical study report.

### **9.1. General Considerations**

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum value, and maximum value). Categorical data will be summarized using counts and percentages. All data will be listed in data listings.

### **9.2. Study Population**

#### **9.2.1. Subject Disposition**

The number and percentage of subjects who enter and complete the study will be presented by group (ie, Part 1 subjects, Part 2 subjects, and extension study subjects). Subjects who fail to complete the study will be summarized and categorized by reason for termination (lost to follow-up, AE, etc.). In addition, the numbers of subjects in each analysis set will be summarized by group

#### **9.2.2. Demographic Information and Baseline Characteristics**

Demographics and baseline characteristics will be summarized descriptively by group and will be summarized for each of the defined analysis sets.

#### **9.2.3. Prior and Concomitant Medications**

Medications will be coded according to the current version of the World Health Organization Drug Dictionary. Prior and concomitant medications will be summarized descriptively by group.

#### **9.2.4. Protocol Deviations**

Protocol deviations will be listed by subject and a summary of significant protocol deviations by type will be produced.

#### **9.2.5. Analysis Populations**

**Safety Population:** All subjects who received study drug

**Pharmacokinetic Population:** All subjects who received study drug and provide adequate PK samples to calculate PK parameters

## **9.3. Safety Analyses**

### **9.3.1. Adverse Events**

AE terms will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing an event will be summarized

for each system organ class and preferred term by group. Likewise, AEs will also be tabulated according to intensity and relationship to study drug. Serious AEs, discontinuation due to AEs, and deaths will also be presented and listed separately, including the relationship to study drug.

### **9.3.2. Physical Examinations**

Physical examination findings will be summarized descriptively by group and by study visit. Individual data listings of physical examination findings will be presented for each subject.

### **9.3.3. Vital Signs**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for vital signs. Individual data listings of vital signs will be presented for each subject.

### **9.3.4. Electrocardiograms**

Observed values at baseline and changes from baseline will be summarized descriptively by group and study visit for the ECG parameters, including PR interval and QTc. Individual data listings of ECGs will be presented for each subject. Flags will be attached to QTc values of clinical significance. Individual data listings of clinically significant ECG parameters will also be presented for each subject.

### **9.3.5. Clinical Laboratory Assessments**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for the clinical laboratory results. Individual data listings of clinical laboratory results will be presented for each subject. Shift tables based on normal ranges will also be presented for select chemistry and hematology laboratory parameters. Flags will be attached to values outside of the laboratory's reference limits along with the PI's assessment of clinical significance. Clinically significant laboratory values will be summarized separately by group and study visit, and individual data listings of clinically significant laboratory results will also be presented for each subject.

## **9.4. Post-treatment Analyses**

Descriptive summary statistics will be used to summarize post study treatment data (ie, any new malignancy). In addition, the relationship between cytogenetic abnormalities and safety parameters may be explored.

## **9.5. Pharmacokinetic Analyses**

### **9.5.1. Part 1**

Plasma concentrations based on the radioactivity and mass spectrometry (MS) ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

### **9.5.2. Part 2**

Whole blood and plasma concentrations based on the radioactivity and MS ion intensity and, if appropriate, the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

### **9.6. Determination of Sample Size**

The sample size of 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) is not based on statistical considerations and instead represents a balance between the number of subjects exposed and accounts for interindividual variability. Enrollment may be extended to replace subjects discontinued during the study ([Section 4.4.1](#)).

### **9.7. Data Monitoring**

An external Data Safety Monitoring Board will not be established for this study. The Sponsor will monitor safety throughout the project through the following efforts:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of nonserious AEs as they are recorded in the eCRF or appear in the source documents at the study center
- Periodic teleconferences with the PI to share experiences and ensure communication

Findings discovered to have immediate implication for the management of subjects on study treatment will be communicated to the PI in the timeframe associated with unexpected and drug-related SAEs.

Safety surveillance will include routine monitoring of clinical laboratory results, physical examination findings, vital signs, AE reporting, and ECG monitoring.

## **10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **10.1. Study Monitoring**

Before the study center can enter a subject into the study, a representative of the Sponsor or a designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or a representative will have regular contacts with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented in eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met the criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### **10.2. Audits and Inspections**

Authorized representatives of the Sponsor, a regulatory authority, an IEC, or an IRB may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

### **10.3. Ethics Committee**

The PI must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study, including the subject ICF and recruitment materials, must be maintained by the PI and made available for inspection.

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## 11. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its representative may conduct a quality assurance audit. Refer to [Section 10.2](#) for more details regarding the audit process.

## **12. ETHICS**

### **12.1. Ethics Review**

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The PI must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### **12.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsor's policy on Bioethics.

### **12.3. Written Informed Consent**

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

## **13. DATA HANDLING AND RECORDKEEPING**

### **13.1. Inspection of Records**

The Sponsor or its representative will be allowed to conduct study center visits at the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **13.2. Retention of Records**

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **14. PUBLICATION POLICY**

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

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## 15. LIST OF REFERENCES

- Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009 Jul 30;114(5):937-51.
- Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245-51.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361(2):123-34.
- Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-61.
- Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res*. 2012;18(6):1726-34.
- Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-92.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
- Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19(5):1519-38.
- Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program*. 2007:172-8.
- TESARO, Inc. Niraparib. Investigator's brochure, Version 3.0. Waltham (MA); 2014. 115 p.
- Thompson JL and Crossman RR. Drug-induced QT prolongation. *US Pharm*. 2007;32(2):44-50.
- United States Department of Health and Human Services (HHS). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. 2009 [cited 30 Jan 2014]. Available from: [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE\\_4.02\\_2009-09-15\\_QuickReference\\_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf).
- United States Department of Health and Human Services (HHS), Food and Drug Administration, Center for Drug Evaluation and Research. Draft guidance. Drug interaction studies – Study design, data analysis, implications for dosing, and labeling recommendations. February 2012 [cited 04 Feb 2014]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>.
- CredibleMeds. Available at: <https://www.crediblemeds.org>

US Pharmacist. Drug-induced QT prolongation page. Available at:  
[http://www.uspharmacist.com/content/d/featured\\_articles/c/10396/](http://www.uspharmacist.com/content/d/featured_articles/c/10396/). Accessed 12 November 2013.

Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. *Ann Pharmacother*. 2013;47(10):1330-41.

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## 16. APPENDICES

### 16.1. Drugs Associated with QT Prolongation and Torsades de Pointes (TdP)

Table 12: Select Drugs Associated with QT prolongation and TdP

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Doxepin	Droperidol	Sumatriptan
Quinidine	Gatifloxacin		Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin		Thioridazine	Arsenic
Dofetilide	Clarithromycin		Ziprasidone	Dolasetron
Ibutilide	Erythromycin			Methadone
	Ketoconazole*			
	Itraconazole			

\*Topical use allowed for ketoconazole

## 16.2. Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Reference: [Oken et al, 1982](#)

1.

**TITLE PAGE**



**Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer**

**EudraCT No:** 2014-002011-41

**Sponsor:** TESARO, Inc.

1000 Winter Street, Suite 3300  
Waltham, MA 02451 USA

PI [REDACTED] MD, MPH  
Senior Medical Director

PI [REDACTED] MD, PhD  
PI [REDACTED], NL

PI [REDACTED]  
PPD

929 North Front Street  
Wilmington, NC 28401 USA

**TESARO Medical Monitor:**

**Principal Investigator:**

**Contract Research Organization:**

**Version of Protocol:**

3.0

**Original Final Protocol Date:**

28 May 2014

**Amendment 1:**

04 December 2014

**Amendment 2:**

17 March 2015

This clinical investigation will be conducted according to this clinical protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki (Version 2008), and with other applicable regulatory requirements.

**Confidentiality Statement**

All information contained in this document is privileged and confidential to TESARO. Any distribution, copying, or disclosure is strictly prohibited without prior written approval by TESARO.

## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

### Declaration of the Principal Investigator

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

**Principal Investigator**

PI

Name:

Title:

Institution:

PI

Date

03-04-2015

## SPONSOR SIGNATURE PAGE

### Declaration of Sponsor or Responsible Medical Expert

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

#### Sponsor Signatory

PI  
PI

MD<sup>PI</sup>

Senior Medical Director  
TESARO, Inc.

20 March 2015

Date

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> TESARO, Inc.	
<b>Name of Investigational Product:</b> Niraparib	
<b>Name of Active Ingredient:</b> Niraparib	
<b>Title of Study:</b> Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer (Protocol Number PR-30-5015-C)	
<b>Study Center(s):</b> A single study center in the Netherlands	
<b>Principal Investigator:</b> PI, MD, PhD <b>Investigators:</b> Not applicable	
<b>Studied Period (years):</b> Estimated date first subject enrolled: February 2015 Estimated date last subject completed: December 2015	<b>Phase of Development:</b> 1
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"><li>To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer</li></ul> <b>Secondary:</b> <ul style="list-style-type: none"><li>To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer</li><li>To evaluate the safety and tolerability of niraparib in subjects with cancer</li></ul>	
<b>Methodology:</b> This is an open-label study with 2 parts, plus an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP). <b>Part 1:</b> The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to	

the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu$ Ci of radioactivity ( $3 \times 100$ -mg capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu$ Ci of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. Participation in Part 2 of the study may extend beyond Day 22 if the amount of radioactivity found in the Day 22 urine or fecal samples is higher than 0.1% of the dose given. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm$  24 hours of the final urine or fecal sample (when both urine and fecal radioactivity is <0.1% of the dose given).

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in

**Table 6.** The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [ $3 \times 100$ -mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments and PK blood sampling. No fasting period is required during the extension study. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject ([Section 7.4](#)). Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

**Number of Subjects (planned):**

**Part 1:** 6 subjects

**Part 2:** 6 subjects

Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

**Diagnosis and Main Criteria for Inclusion:**

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL} (5.6 \text{ mM})$
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) **or** a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN **or** direct bilirubin  $\leq 1 \times$  ULN
  - f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
8. Subject is able to take oral medications.

**Exclusion Criteria:**

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered "controlled," the subject must have undergone treatment (eg, radiation or chemotherapy at least

- 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
4. Subject has known hypersensitivity to the components of niraparib.
  5. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
  6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
  7. Subject received (or is anticipated to receive) a platelet transfusion within 4 weeks of study drug administration.
  8. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
  9. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
  10. Subject is immunocompromised with an active event and is being treated with medications.
  11. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
  12. Subject has a baseline corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.
  13. Subject is receiving concomitant medication(s) that prolong QTc ([Appendix 20.1](#)).
  14. Subject is starting chemotherapy within 3 weeks of study drug administration.
  15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
  16. Subject has a history of illicit drug use.
  17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
  18. Subject is currently participating in another clinical study and has received an investigational drug, or has participated in a clinical study and has received an investigational drug within 21 days of study drug administration.
  19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months prior to study drug administration (for subjects participating in Part 1) or within 30 days prior to study drug administration (for subjects participating in Part 2).

<p><b>Investigational Product, Dosage and Mode of Administration:</b></p> <p><b>Part 1:</b> Niraparib 300 mg (<math>3 \times 100\text{-mg}</math> capsules) orally and [<math>^{14}\text{C}</math>]-niraparib 100 <math>\mu\text{g}</math> (1 <math>\mu\text{Ci}</math> total radioactivity) intravenously</p> <p><b>Part 2:</b> [<math>^{14}\text{C}</math>]-niraparib 300 mg (<math>3 \times 100\text{-mg}</math> capsules; <math>3 \times 33.3 \mu\text{Ci}</math> radioactivity [100 <math>\mu\text{Ci}</math> total radioactivity]) orally</p> <p><b>Extension study:</b> Niraparib 300 mg (<math>3 \times 100\text{-mg}</math> capsules) orally</p>
<p><b>Duration of Treatment:</b></p> <p><b>Part 1:</b> Administration of a single oral dose, followed by a 15-minute IV infusion 2 hours after administration of the single oral dose</p> <p><b>Part 2:</b> Administration of a single oral dose</p> <p><b>Extension Study:</b> QD administration until treatment discontinuation</p>
<p><b>Reference Therapy, Dosage and Mode of Administration:</b></p> <p>None.</p>
<p><b>Criteria for Evaluation:</b></p> <p><b>Pharmacokinetics:</b></p> <p><b>Part 1:</b> Plasma niraparib concentrations will be used to determine the following PK parameters: maximum observed plasma concentration (<math>C_{\max}</math>); time to reach <math>C_{\max}</math> (<math>T_{\max}</math>); and area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration (<math>AUC_{0-\text{last}}</math>); and if the data allow: AUC from time 0 to infinity (<math>AUC_{0-\infty}</math>); apparent oral volume of distribution (<math>Vd/F</math>); apparent oral clearance (<math>CL/F</math>); and half-life (<math>t_{1/2}</math>). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.</p> <p><b>Part 2:</b> Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters: <math>C_{\max}</math>, <math>T_{\max}</math>, and <math>AUC_{0-\text{last}}</math>. The plasma niraparib concentration will be used to determine the following PK parameters: <math>C_{\max}</math>, <math>T_{\max}</math>, and <math>AUC_{0-\text{last}}</math>, and if the data allow: <math>AUC_{0-\infty}</math>, <math>Vd/F</math>, <math>CL/F</math>, and <math>t_{1/2}</math>. Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period, <math>A_e</math> (day), and total amount of drug excreted in the urine, <math>A_e</math> (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption (<math>f</math>), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.</p> <p><b>Extension Study:</b> Plasma niraparib concentrations will be used to determine the following PK parameters: <math>C_{\max}</math>, <math>T_{\max}</math>, <math>AUC_{0-\text{last}}</math>, <math>AUC_{0-\infty}</math>, and <math>t_{1/2}</math>.</p> <p><b>Safety:</b></p> <p>Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.</p>

**Statistical Methods:**

**Pharmacokinetics:**

For Part 1, plasma concentrations based on the radioactivity and mass spectrometry (MS) ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure. For Part 2, whole blood and plasma concentrations based on the radioactivity and MS ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented. For the extension study, plasma concentrations of niraparib based on MS ion intensity and, if appropriate, the derived PK parameters will be summarized using descriptive statistics and graphics.

**Safety:**

All AEs will be listed and tabulated. Physical examination findings, vital signs, ECG parameters, and clinical laboratory results will be listed and summarized using descriptive statistics.

**Table 1: Schedule of Assessments: Part 1**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X												X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X <sup>c</sup>	X	X	X <sup>d</sup>	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>d</sup>	X												
Clinical laboratory assessment <sup>e</sup>	X <sup>f</sup>												X X
Serum pregnancy test (women of childbearing potential)	X												X
Electrocardiogram (12-lead) <sup>g</sup>	X		X										X
ECOG performance status	X												X <sup>h</sup>
Confirm diagnosis with CT scan <sup>i</sup>	X												
Subject confinement		X <sup>c</sup>	X	X	X	X							
Niraparib oral administration <sup>j</sup>			X										
[ <sup>14</sup> C]-niraparib IV infusion <sup>k</sup>			X										

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Pharmacokinetic blood sampling <sup>l</sup>			X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>m</sup>	X	X <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous

<sup>a</sup> Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>c</sup> If subject comes to the center and/or chooses to be admitted on Day -1.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>f</sup> Must occur within 72 hours prior to dosing.

<sup>g</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>h</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit.

Discontinued subjects will be followed for all relevant safety parameters (see [Section 12](#)).

<sup>i</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>j</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>k</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>l</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [±2 min], 1.5 [±2 min], 2 [within 1 min prior to IV infusion], 2.125 [±1 min], 2.25 [within 1 min post-infusion], 2.33 [±1 min], 2.66 [±1 min], 3 [±2 min], 4 [±5 min], 6 [±5 min], and 12 hours [±15 min] postdose), Day 2 (24 [±1] hours postdose), Day 3 (48 [±2] hours postdose), Day 4 (72 [±4] hours postdose), Day 5 (96 [±4] hours postdose), Day 7 (144 [±4] hours postdose), Day 9 (192 [±8] hours postdose), Day 11 (240 [±12] hours postdose), Day 13 (288 [±12] hours postdose), Day 15 (336 [±12] hours postdose), and Day 22 (504 [±12] hours postdose).

<sup>m</sup> New serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit

**Table 2: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																	
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup> End of Part 2
Informed consent	X																	
Subject demographics and baseline characteristics	X																	
Medical history and cancer history	X																	
Inclusion/exclusion criteria	X																	
Physical examination	X																	X
Height (cm)	X																	
Weight (kg)	X																	X
Body mass index (kg/m <sup>2</sup> )	X																	
Vital signs <sup>c</sup>	X	X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X			X	X
HBV/HCV/HIV screening <sup>e</sup>	X																	
Clinical laboratory assessments <sup>f</sup>	X <sup>g</sup>																X	X
Serum pregnancy test (women of childbearing potential)	X																	X <sup>h</sup>
Electrocardiogram (12-lead) <sup>i</sup>	X		X															X
ECOG performance status	X																	X <sup>h</sup>
Confirm diagnosis with CT scan <sup>j</sup>	X																	
Subject confinement		X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X				
[ <sup>14</sup> C]-niraparib oral administration <sup>k</sup>			X															
Pharmacokinetic blood sampling <sup>l</sup>			X	X	X	X	X	X	X	X			X		X		X	X <sup>l</sup>

Assessment or Procedure	Day Relative to First Dose of Study Drug																		
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup>	End of Part 2
Blood sample for metabolite profiling <sup>m</sup>			X	X	X	X	X	X		X			X				X	X	
Urine collection <sup>n</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fecal collection <sup>o</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/concomitant medication and AE monitoring <sup>p</sup>	X	X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X				X	X	

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote n and Footnote o), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped. Note that only urine/fecal and PK blood collections may extend beyond Day 22; other assessments do not need to be repeated.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>d</sup> If subject comes to the center and/or chooses to be admitted on Day -1.

<sup>e</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>f</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>g</sup> Must occur within 72 hours prior to dosing.

<sup>h</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see Section 12).

<sup>i</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>j</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>k</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity (3 × 100-mg capsules, labeled active pharmaceutical ingredient [3 x 33.3 µCi of radioactivity]), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<sup>l</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm$ 2 min], 1.5 [ $\pm$ 2 min], 2 [ $\pm$ 2 min], 3 [ $\pm$ 2 min], 4 [ $\pm$ 5 min], 6 [ $\pm$ 5 min], and 12 hours [ $\pm$ 15 min] postdose), Day 2 (24 [ $\pm$ 1] hours postdose), Day 3 (48 [ $\pm$ 2] hours postdose), Day 4 (72 [ $\pm$ 4]

hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose). Participation in Part 2 of the study may extend beyond Day 22 if the amount of radioactivity found in the Day 22 urine or fecal samples is higher than 0.1% of the dose given. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm$  24 hours of the final urine or fecal sample (when both urine and fecal radioactivity is <0.1% of the dose given).

<sup>m</sup> Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>n</sup> Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

<sup>o</sup> Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

<sup>p</sup> New serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit.

**Table 3: Schedule of Assessments: Open-Label Extension Study**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c</sup>
		Day 1	Day 8	Day 15	Day 22		
Inclusion/exclusion criteria	X						
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>d</sup>	X		X	X	X	X	X
Complete blood count (CBC) <sup>e</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>f</sup>	X			X		X	X
Pregnancy test (women of childbearing potential) <sup>g</sup>	X					X	X
Study drug dispensed/collected <sup>h</sup>		X				X	X
Electrocardiogram (12-lead) <sup>i</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>j</sup>		X				X	
Niraparib oral administration (in-house) <sup>k</sup>		X	X	X	X	X	
Concomitant medication and AE monitoring <sup>l</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

a Upon completion of Part 1 or 2 of the study (or if subject is non-evaluable for PK in Part 1 or 2), subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Investigator with consideration for a reduced dose as described in **Table 6**. The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which

must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit.

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days. Visits (except Cycle 1) will continue approximately every 4 weeks until treatment discontinuation

<sup>c</sup> The EOT visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)). If the subject discontinues due to disease progression, then the CT scan (taken per standard of care) closest to the time of progression (EOT) should be provided.

<sup>d</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.

<sup>e</sup> The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.

<sup>f</sup> Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.

<sup>g</sup> A serum pregnancy test will be conducted at the Screening Visit and at EOT. A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4/Day 1, Cycle 7/Day 1, etc.).

<sup>h</sup> Subjects will take 300 mg (3  $\times$  100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. No fasting period is required during the extension study. No new capsules will be dispensed at EOT.

<sup>i</sup> Subjects will have a 12-lead ECG at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at EOT.

<sup>j</sup> Blood samples for PK analysis will be collected at the following times: Cycle 1/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).

<sup>k</sup> Niraparib is self-administered daily, except on study visit days. On days of study visits (eg, Cycle 1, Day 1, 8, 15, and 22; Cycle n, Day 1) subjects should refrain from taking niraparib until after clinical assessments are performed.

<sup>l</sup> New serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit.

3.

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#### 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 4: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event
A <sub>e</sub> (day)	Amount of drug excreted in the urine in a 24-hour period
A <sub>e</sub> (total)	Total amount of drug excreted in the urine
ALT	Alanine aminotransferase
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC <sub>0-inf</sub>	Area under the plasma concentration-time curve from time 0 to infinity
AUC <sub>0-last</sub>	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
CA-125	Cancer antigen 125
CBC	Complete blood count
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent oral clearance
C <sub>max</sub>	Maximum observed plasma concentration
CNS	Central nervous system
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	Cytochrome P450 1A2
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
f	Extent of absorption
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HER2	Human epidermal growth factor 2
hERG	Human Ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HR	Homologous recombination
IBTs	Investigator's brochure
IC <sub>20</sub>	20% maximum inhibitory concentration
IC <sub>50</sub>	50% maximum inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LSC	Liquid scintillation counting
MedDRA	Medical Dictionary for Regulatory Activities
MS	Mass spectrometry
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
P-gp	P-glycoprotein
PARP	Poly (adenosine diphosphate-ribose) polymerase
PI	Principal Investigator
PK	Pharmacokinetic
QD	Once a day
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
t <sub>½</sub>	Half-life

Abbreviation or Specialist Term	Explanation
TEAE	Treatment-emergent adverse event
$T_{max}$	Time to reach maximum observed plasma concentration
ULN	Upper limit of normal
Vd/F	Apparent oral volume of distribution

## 5. INTRODUCTION

### 5.1. Niraparib

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally active poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor with nanomolar potency that is being developed for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway or that are driven by PARP-mediated transcription factors.

#### 5.1.1. DNA Repair, Cancer, and PARP Inhibition

The PARP-1 and -2 enzymes, which are zinc-finger DNA-binding enzymes, play a crucial role in DNA repair. Upon formation of single-strand DNA breaks, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones, various DNA repair proteins, and PARP itself, which results in chromatin relaxation and fast recruitment of DNA repair factors that access and repair DNA breaks.

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of tumor cells than on normal cells. Therefore, a hypothesis is that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways.

Clinical studies have shown that PARP inhibitors have antitumor activity in certain types of cancer (Fong et al, 2009; Audeh et al, 2010; Gelmon et al, 2011; Kummar et al, 2012; Ledermann et al, 2012). Nonclinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with homozygous inactivation of either *BRCA-1* or *BRCA-2*; these breast cancer genes are known to be important in the HR DNA repair pathway. Germline mutations of *BRCA-1* and -2 are found in the majority of subjects with inherited breast or ovarian cancer. Inactivation of *BRCA-1* and -2 by mechanisms other than mutations, including somatic mutations and gene silencing by promoter hypermethylation, occurs in a significant portion of several sporadic cancers. In particular, for ovarian cancer, somatic *BRCA-1* or -2 mutations are found in 10% to 15% of all epithelial ovarian carcinomas, and strongly reduced expression of *BRCA-1* has been observed in a significant portion of sporadic ovarian cancers. Collectively, up to 40% to 60% of ovarian cancers might be responsive to PARP inhibitors as a consequence of defects in the BRCA-HR pathway, indicating a great potential for this approach in the therapy of ovarian cancer.

#### 5.1.2. Niraparib Nonclinical Studies

Niraparib inhibits normal DNA repair mechanisms and induces synthetic lethality when administered to cells with HR defects. In a *BRCA-1* mutant xenograft study in mice, niraparib dosed orally caused tumor regression, which was mirrored by a greater than 90% reduction in

tumor volume compared to control. In a *BRCA-2* mutant xenograft study in mice, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib was evaluated for its potential effects on cardiovascular and neurological function using several experimental safety pharmacology models. Niraparib inhibited the human Ether-à-go-go-related gene (hERG) current with a 50% maximal inhibitory concentration ( $IC_{50}$ ) value of 10  $\mu$ M and a 20% maximal inhibitory concentration ( $IC_{20}$ ) value of 3.8  $\mu$ M. Niraparib was administered intravenously during 3 sequential 30-minute periods at 1, 3, and 10 mg/kg to determine the effect of niraparib on cardiovascular function in 3 anesthetized dogs. Niraparib had no effect on the corrected QT interval (QTc; average plasma concentration  $\leq$ 15.3  $\mu$ M at 10 mg/kg). Mean arterial pressure and heart rate were increased at all doses evaluated, but the QRS cardiac interval was only increased at 10 mg/kg. Niraparib had no effect on neurological function in conscious mice at a single oral dose of 100 mg/kg.

The pharmacokinetics (PK) of niraparib in male Sprague-Dawley rats were determined following intravenous (IV; 3 mg/kg) and oral (5 mg/kg) administration. In male beagle dogs, PK studies were conducted following IV (1 mg/kg) and oral (3 mg/kg) administration. Following IV administration, niraparib demonstrated moderate-to-high clearance (28 and 31 mL/min/kg), a high volume of distribution (6.9 and 12.3 L/kg), and moderate terminal half-lives (3 and 6 hours) in rats and dogs, respectively. The oral bioavailability of niraparib was reasonable in both species (approximately 27% in rats and 57% in dogs).

Niraparib was investigated in 1-month oral toxicity studies in order to support daily dosing of the compound in humans, where niraparib was administered to rats and dogs by oral gavage once a day (QD) for up to 4 weeks followed by an approximately 2-week recovery period. Overall, nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. In the 1-month repeat-dose toxicity study in rats, mortality and physical signs were limited to the high dose (50 mg/kg/day). All changes observed at 50 mg/kg/day were resolved at the end of the 2-week recovery period or demonstrated reversibility, except for minimal treatment-related arterial hypertrophy in the heart and increased trabecula in the bone. At 10 mg/kg/day, there were no treatment-related changes other than increased urine volume in males. Based on these findings, the no observed adverse effect level (NOAEL) in the rat study was 10 mg/kg/day. The dose causing severe irreversible toxicity and death was 50 mg/kg/day. In the dog, decreases in hematology values were observed at a dose of 15 mg/kg/day, and all hematology changes seen during the dosing phase were resolved at the end of the recovery period. Although a decrease in amount of spermatogenic epithelium was observed after 1-month dosing at 6 mg/kg/day and 15 mg/kg/day and was not resolved at the end of the 2-week recovery period, the continued presence of spermatogenic epithelium supports that this change would eventually resolve. Therefore, based on these findings, the NOAEL for the dog study was 3 mg/kg/day.

The niraparib nonclinical studies are described in detail in the [Investigator's Brochure \(IB\)](#); version 3.0, 09 April 2014).

### **5.1.3. Niraparib Clinical Studies**

The niraparib clinical studies are described in detail in the [IB](#) (version 3.0, 09 April 2014).

### 5.1.3.1. Phase 1 Studies

Niraparib has been evaluated in a series of Phase 1 clinical studies in subjects with solid tumors. For these studies, niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide. As of 15 November 2013, 144 subjects have been treated with oral niraparib at doses up to 400 mg QD in Phase 1 studies, and treatment with niraparib has been generally well tolerated.

The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were (n=144): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), rash (10.4%), dizziness (9.7%), electrocardiogram (ECG) QT prolonged (9.7%), pyrexia (9.7%), abdominal distension (9.0%), urinary tract infection (9.0%), weight decreased (9.0%), abdominal pain lower (8.3%), alopecia (8.3%), neoplasm malignant (8.3%), dry mouth (7.6%), hypoalbuminemia (7.6%), musculoskeletal pain (7.6%), stomatitis (7.6%), arthralgia (6.9%), blood creatinine increase (6.9%), chills (6.9%), dyspepsia (6.9%), hypomagnesemia (6.9%), paresthesia (6.9%), aspartate aminotransferase (AST) increased (6.3%), dehydration (6.3%), musculoskeletal chest pain (6.3%), neck pain (6.3%), alanine aminotransferase (ALT) increased (5.6%), dysgeusia (5.6%), myalgia (5.6%), and palpitations (5.6%).

The most commonly reported drug-related (>5.0%) AEs (all grades) in the clinic were (n=129): fatigue (45.1%), nausea (42.4%), anemia (41.0%), thrombocytopenia (32.6%), decreased appetite (23.6%), neutropenia (22.2%), vomiting (22.2%), constipation (19.4%), leukopenia (18.1%), diarrhea (10.4%), insomnia (8.3%), dyspnea (6.9%), ECG QT prolonged (6.9%), headache (6.3%), stomatitis (6.3%), hyponatremia (5.6%), and alopecia (5.6%).

#### 5.1.3.1.1. Study PN001

The maximum tolerated dose (MTD) of niraparib dosed orally QD was determined to be 300 mg in subjects with advanced solid tumors or hematologic malignancies. The dose-limiting toxicity for niraparib is thrombocytopenia, with Grade 4 thrombocytopenia reported in 2 of 6 subjects treated at the 400-mg dose level. For the 44 subjects treated at the MTD, 21 subjects experienced thrombocytopenia, 16 subjects experienced neutropenia, and 34 subjects experienced anemia.

During routine safety monitoring, 12 of 104 subjects reported AEs of prolonged QTc (6 subjects experienced a Grade 1 event, 5 subjects experienced a Grade 2 event, and 1 subject experienced a Grade 3 event). Preliminary evaluation showed 8 of these subjects (7.7%) had QT prolongation that was assessed as at least possibly related to study drug. Of these 8 subjects, 7 received 300 mg of niraparib QD and 1 received 210 mg of niraparib QD. A total of 8 subjects exceeded a 30-msec change from baseline during the study, with the maximum being 70 msec. Given that these were spontaneous reports, and not part of a controlled QTc evaluation, it would be difficult to assess the relationship to niraparib. Until a more rigorous evaluation of QTc can be conducted, subjects should be evaluated for QTc prolongation.

A preliminary analysis of plasma drug concentration profiles indicated that the maximum observed plasma concentration ( $C_{max}$ ) after oral dosing occurred at approximately 3 hours. There was an approximate 3- to 4-fold accumulation in the area under the plasma concentration-time curve (AUC),  $C_{max}$ , and plasma concentration at 24 hours postdose from Cycle 1/Day 1 to Cycle 2/Day 1. Mean apparent terminal half-life ( $t_{1/2}$ ) ranged from 32.8 to 46.0 hours over the 60- to 400-mg dose range. PK parameters appeared to be dose-proportional.

Although efficacy was not the primary objective for this Phase 1 study, antitumor activity was observed in subjects taking niraparib as monotherapy at oral dose levels ranging from 60 to 400 mg. Based on Investigator evaluation using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or cancer antigen 125 (CA-125) criteria, an overall response rate of 13% was observed for all subjects in this study. Analysis of the 20 *BRCA* mutant ovarian cancer subjects enrolled in the study demonstrated that this group showed a 35% overall response rate according to RECIST version 1.1 and/or CA-125 criteria.

#### **5.1.3.2. Phase 3 Studies**

The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline *BRCA* mutation breast cancer subjects (PR-30-5010-C; BRAVO) and to platinum-sensitive ovarian cancer subjects (PR-30-5011-C; NOVA). A total of 55 subjects had been randomized in the Phase 3 clinical study program as of 07 January 2014. Preliminary results from 15 subjects who completed the PR-30-5011-C study suggest administration of niraparib with food is expected to have a negligible effect on the PK of niraparib. Of the 16 subjects enrolled in the PR-30-5011-C study as of 15 November 2013, the most commonly reported AEs were gastrointestinal disorders (constipation, nausea, and vomiting) and metabolism and nutrition disorders (decreased appetite).

#### **5.1.4. Risks and Benefits**

The potential benefit of niraparib treatment for patients with cancer is tumor regression.

Nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. The most commonly reported AEs in the clinic for the Phase 1 studies, where niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide, were (Section 5.1.3.1): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), and rash (10.4%). The Investigator should monitor subjects closely for these AEs.

As Phase 1 studies have shown that niraparib is safe and well tolerated, the potential benefits outweigh the potential risks.

When taking niraparib, caution should be used when also taking medications that are inducers of cytochrome P450 1A2 (CYP1A2) or inhibitors or inducers of P-glycoprotein (P-gp; Section 9.2).

The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs ([Section 9.2](#)).

## **5.2. Rationale for Current Study**

This is an open-label study with 2 parts, plus an extension study following completion of Parts 1 or 2, that is being conducted in approximately 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) with cancer to examine the absorption, metabolism, excretion, and absolute bioavailability of niraparib. This study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

The oral bioavailability of niraparib has been determined in rats and dogs ([Section 5.1.2](#)), but has yet to be determined in human subjects, including those with cancer. Therefore, this study will examine the absolute oral bioavailability of niraparib and the absorption, metabolism, excretion, and mass balance of oral [ $^{14}\text{C}$ ]-niraparib in subjects with cancer.

The oral dose of niraparib used in this study is 300 mg, which is the MTD of niraparib ([Section 5.1.3.1.1](#)). A total of 144 subjects have been treated with niraparib up to 400 mg QD in Phase 1 studies, and the 300-mg daily dose of niraparib is considered safe and generally well tolerated (IB version 3.0, 09 April 2014). The 300-mg daily dose of niraparib is currently being administered in 2 Phase 3 studies ([Section 5.1.3.2](#)).

This study will be the first-in-human administration of the IV formulation of niraparib. Data from the nonclinical studies did not demonstrate any safety issues that would preclude testing of IV niraparib in humans, and a microdose (100  $\mu\text{g}$ ) of niraparib is being administered in the current study.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Primary Objective**

- To determine the absolute bioavailability of niraparib by using an IV niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer.

### **6.2. Secondary Objectives**

- To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer.
- To evaluate the safety and tolerability of niraparib in subjects with cancer.

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is an open-label study with 2 parts, plus an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP).

**Part 1:** The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100  $\mu\text{g}$  niraparib, containing approximately 1  $\mu\text{Ci}$  of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu\text{Ci}$  of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu\text{Ci}$  of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. Participation in Part 2 of the study may extend beyond Day 22 if the amount of radioactivity found in the Day 22 urine or fecal samples is higher than 0.1% of the dose given. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm 24$  hours of the final urine or fecal sample (when both urine and fecal radioactivity is <0.1% of the dose given).

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments and PK blood sampling. No fasting period is required during the extension study. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject ([Section 7.4](#)). Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

The schedule of assessments for Part 1, Part 2, and the extension study are presented in [Table 1](#), [Table 2](#), and [Table 3](#), respectively.

## 7.2. Number of Subjects

There will be 6 subjects in Part 1 of the study and 6 subjects in Part 2 of the study. Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

## 7.3. Treatment Assignment

At the Screening Visit, subjects will be offered the option to participate in either Part 1 or Part 2 of the study until 1 part of the study is fully enrolled, at which time subjects can only be screened for the remaining part of the study, or for future replacements ([Section 8.4.1](#)). Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

#### 7.4. Dose Adjustment Criteria

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject. Treatment must be interrupted for any nonhematologic National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.02; HHS 2009) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days of dose interruption, at the Investigator's discretion the subject may restart treatment with niraparib, but with a dose level reduction according to Table 5 if prophylaxis is not considered feasible. Upon re-challenge, if the event recurs at a similar or worse grade, then treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted.

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 28-day dose interruption period, and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

**Table 5: Niraparib Dose Reductions for Nonhematologic Toxicities**

Event <sup>a</sup>	Dose <sup>b</sup>
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE $\geq$ 28 days	Discontinue study drug

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; QD, once a day; SAE, serious adverse event.

<sup>a</sup> Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject.

<sup>b</sup> Dose not to be decreased below 100 mg QD.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts, as outlined in Table 6.

**Table 6: Niraparib Dose Modification/Reduction for Hematologic Toxicities**

Event	Dose Modification
Platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq$ 100,000/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at the same dose or a reduced dose based on clinical judgment.

Event	Dose Modification
Second occurrence of platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq$ 100,000/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count <75,000/ $\mu$ L <sup>a</sup>	Study drugs must be interrupted until platelet counts are $\geq$ 100,000/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophils <1000/ $\mu$ L	Study drugs must be interrupted until neutrophil counts are $\geq$ 1500/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin <8 g/dL	Study drugs must be interrupted until hemoglobin is $\geq$ 9 g/dL with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviation: CBC, complete blood count.

<sup>a</sup> For subjects with a platelet count  $\leq$ 10,000/ $\mu$ L, a prophylactic platelet transfusion per guidelines may be considered (Schiffer et al., 2001; Slichter, 2007). For subjects taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as  $\leq$ 20,000/ $\mu$ L

If dose interruption or modification is required at any point during the study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for CBC will be required for an additional 28 days after the AE has been resolved to the specified levels, after which monitoring every 28 days may resume. Weekly blood draws for CBC can be collected either at the study center or local laboratories. If the hematologic toxicity has not recovered to the specified levels within 28 days of the dose interruption period and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

For major surgery while on treatment, up to 28 days of drug interruption is allowed.

Once the dose of study drug has been reduced, any re-escalation must be discussed with the Medical Monitor.

All dose interruptions and reductions (including any missed doses) and the reasons for the interruptions and reductions will be recorded in the electronic case report form (eCRF).

## 7.5. Criteria for Study Termination

If in the opinion of the Investigator or Sponsor there is reasonable or sufficient cause, this study may be prematurely terminated at any time. Written notification documenting the reason for study termination will be provided to the Investigator or Sponsor by the terminating party. Circumstances that may warrant termination include study center performance issues, a potential new finding with the study drug, or changes in the development program. See [Section 8.4](#) for subject withdrawal criteria. Additional circumstances include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects

- Failure to enroll subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of study drug

Should the study be stopped prematurely, all study materials must be returned to the Sponsor or be disposed of according to the Sponsor's specifications.

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## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - Platelets  $\geq 100,000/\mu\text{L}$
  - Hemoglobin  $\geq 9 \text{ g/dL} (5.6 \text{ mM})$
  - Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
8. Subject is able to take oral medications.

### 8.2. Subject Exclusion Criteria

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.

3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
4. Subject has known hypersensitivity to the components of niraparib.
5. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
7. Subject received (or is anticipated to receive) a platelet transfusion within 4 weeks of study drug administration.
8. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject’s participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
9. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
10. Subject is immunocompromised with an active event and is being treated with medications.
11. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
12. Subject has a baseline corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.
13. Subject is receiving concomitant medication(s) that prolong QTc ([Appendix 20.1](#)).
14. Subject is starting chemotherapy within 3 weeks of study drug administration.
15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
16. Subject has a history of illicit drug use.
17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.

18. Subject is currently participating in another clinical study and has received an investigational drug, or has participated in a clinical study and has received an investigational drug within 21 days of study drug administration.
19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months prior to study drug administration (for subjects participating in Part 1) or within 30 days prior to study drug administration (for subjects participating in Part 2).

### **8.3. Restrictions During Study**

Restrictions during the study include the following:

1. If sexually active, subjects of reproductive potential and their partners must agree to the use of 2 of the following highly effective forms of contraception throughout their participation in the study and for 90 days after the last dose of study drug:
  - Condom with spermicide and one of the following:
    - Oral contraceptive or hormonal therapy (eg, hormone implants)
    - Placement of an intrauterine device

Acceptable nonhormonal birth control methods include the following:

- Total sexual abstinence
- Vasectomized sexual partner and use of a male condom, with subject assurance that partner received postvasectomy confirmation of azoospermia
- Tubal occlusion and use of a male condom with spermicide
- Intrauterine device and use of a male condom with spermicide

Acceptable hormonal birth control methods with use of a male condom with spermicide include the following:

- Etonogestrel implants (eg, Implanon®, Norplant®)
- Normal and low dose combined oral contraceptive pills
- Norelgestromin/ethynodiol transdermal system
- Intravaginal device (eg, ethynodiol and etonogestrel)
- Cerazette® (desogestrel), which is currently the only highly efficacious progesterone-based pill

2. No other anticancer therapy is permitted during the course of study treatment for any subject. If the subject discontinues study drug, this restriction no longer applies. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

3. Prophylactic cytokine (granulocyte colony-stimulating factor) administration should not be given in the first cycle of the extension study but may be administered in subsequent cycles according to local guidelines.
4. An increased risk of infection with the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown, so live virus and bacterial vaccines should not be administered to subjects in the study.
5. Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to receiving study drug and/or within 6 hours after receiving study drug.
6. Subjects who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.
7. Subjects should try to minimize their exposure to ultraviolet light, including natural or artificial sunlight (tanning beds or ultraviolet A or B treatment), while taking niraparib to avoid any possibility of phototoxicity. If subjects need to be outdoors while taking niraparib, they should wear loose fitting clothes and hats that protect skin from direct sun exposure and discuss other sun protection measures with their physician, such as ultraviolet-protection sunscreen. If a sunburn-like reaction or skin eruption occurs, subjects should contact their physician.
8. Blood transfusions within the first 3 days post study drug administration are permissible if the blood transfusion is <500 mL/day.

#### **8.4. Subject Withdrawal Criteria**

A subject may be discontinued from treatment or from the study for the following reasons:

- AE
  - For the extension study only, a treatment-related CTCAE Grade 3 or 4 AE that has not reverted to CTCAE Grade 1 or less within 28 days of dose interruption. At the Investigator's discretion, following dose interruption (no longer than 28 days), subjects may be considered for dose reductions ([Section 7.4](#)), providing they have not already undergone the maximum number of 2 dose reductions allowed. If a CTCAE Grade 3 or 4 AE recurs upon re-challenging with study drug at the lowest allowable dose, the subject must permanently discontinue treatment.
- Unacceptable toxicity
  - For the extension study only, if the subject experiences a dose interruption or modification because of a hematologic toxicity and the platelet count has not reverted to  $\geq 100,000/\mu\text{L}$  within 28 days of dose interruption, the subject should be discontinued.
- Severe noncompliance with the protocol, as judged by the Investigator and/or Sponsor.
- Subject becomes pregnant

- It is in the best interest of the subject, as judged by the Investigator and/or Sponsor
- Subject withdraws consent
- Sponsor decision to terminate study
- For the extension study only, disease progression and/or clinical criteria per standard of care

Subjects who discontinue from treatment will continue to receive follow-up safety assessments (see [Section 12](#)) as part of the study for 30 days from the last dose, unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the subject, who is at any time and for any reason free to discontinue their participation in the study, without prejudice to further treatment
- Death
- Loss to follow-up

If a subject is lost to follow-up or withdraws from study treatment, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.

#### **8.4.1. Replacement of Subjects**

After consultation between the Sponsor and the Principal Investigator (PI), enrollment may be extended to replace subject(s) discontinued during the study. Replacement subjects will be assigned the next available dosing number for the part of study in which the discontinued subjects were enrolled.

## 9. TREATMENT OF SUBJECTS

### 9.1. Description of Study Drug

The investigational products that will be used in this study are summarized in Table 7.

**Table 7: Investigational Product**

	Investigational Product		
<b>Product Name</b>	niraparib	[ <sup>14</sup> C]-niraparib IV solution	[ <sup>14</sup> C]-niraparib
<b>Dosage Form</b>	100-mg capsules	sterile solution for IV administration	capsules
<b>Unit Dose</b>	300 mg (3 × 100-mg capsules)	100 µg (1 µCi total radioactivity)	300 mg (3 × 100-mg capsules, 3 x 33.3 µCi of radioactivity [100 µCi total radioactivity])
<b>Route of Administration</b>	oral	IV	oral
<b>Study Phase Taken</b>	Part 1 and Extension	Part 1	Part 2

Abbreviation: IV, intravenous.

### 9.2. Prior and Concomitant Medications

Any medication the subject takes during the study other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication.

All prior and concomitant medications will be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Known prior medications that exclude a subject from participating in the study are described in the Exclusion Criteria ([Section 8.2](#)). Prohibited concomitant medications are described in [Section 8.3](#). Additionally, niraparib has potential to induce CYP1A2. Therefore, subjects should be advised to use caution when taking medications that are also inducers of CYP1A2. Examples of CYP1A2 inducers include montelukast, phenytoin, moricizine, omeprazole, and phenobarbital ([HHS 2012](#)). Niraparib is a substrate for P-gp; therefore, subjects should be advised to use caution when taking medications that are inhibitors or inducers of P-gp. Examples of P-gp inhibitors include the following ([HHS 2012](#)): amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and

verapamil. Examples of P-gp inducers include the following (HHS 2012): avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir-ritonavir. Permitted anti-nausea medications are dexamethasone, aprepitant, and granisetron.

The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs.

### **9.3. Treatment Compliance**

The study staff will maintain an ongoing record of the dispensing and administration of study drug for each subject. For the extension study, subjects will be instructed to return any unused study drug to the study center during their visit on the first day of each cycle or at EOT. Drug accountability will be performed on capsules dispensed versus returned to the study center at each visit and the number of days since the last visit.

### **9.4. Randomization and Blinding**

Subjects will not be randomly assigned and instead may choose in which part of the study to participate ([Section 7.3](#)). This is an unblinded study.

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Study Drug**

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor.

### **10.2. Study Drug Packaging and Labeling**

Niraparib 100-mg capsules (unlabeled active pharmaceutical ingredient) will be packed in high-density polyethylene bottles with child-resistant closures. For the extension study, each dosing container will contain a sufficient number of capsules for 1 treatment cycle. Niraparib will be dispensed to subjects on Day 1 of every cycle of the extension study.

The IV solution and oral capsules will be prepared for dosing by Quotient Clinical from [ $^{14}\text{C}$ ]-niraparib active pharmaceutical ingredient following Good Manufacturing Practices. Information on the preparation, packaging, and labeling of the IV solution (containing approximately 1  $\mu\text{Ci}$  of radioactivity) and oral capsules (containing approximately 100  $\mu\text{Ci}$  of radioactivity per 300-mg dose) of niraparib can be found in the investigational medicinal product dossier.

### **10.3. Study Drug Storage**

The 100-mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 15°C to 25°C. Until study drug is dispensed to the subjects, the study drug will be stored in a suitable container, at storage conditions specified by the Sponsor, in a securely locked area, accessible to authorized personnel only.

Information for storing the IV solution (containing approximately 1  $\mu\text{Ci}$  of radioactivity) and oral capsules (containing approximately 100  $\mu\text{Ci}$  of radioactivity) of niraparib can be found in the investigational medicinal product dossier.

### **10.4. Study Drug Administration**

For Part 1, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100  $\mu\text{g}$  niraparib, containing approximately 1  $\mu\text{Ci}$  of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For Part 2, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu\text{Ci}$  of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu\text{Ci}$  of radioactivity]), on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Subjects will continue fasting until

4 hours after administration of study drug, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For the extension study, 300 mg of niraparib (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) will be administered orally QD until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)); dose interruptions and reductions will be allowed based on treatment side effects ([Section 7.4](#)). No fasting period is required during the extension study. Subjects will be instructed to take the niraparib dose at the same time of day, preferably in the morning. The first dose will be administered at the study center. Subjects must swallow and not chew the capsules, and the consumption of water is permissible. On days of study visits (eg, Cycle 1, Day 1, 8, 15, and 22; Cycle n, Day 1), subjects should refrain from taking niraparib until after clinical assessments are performed.

### **10.5. Study Drug Accountability**

The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes the subject number, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as “returned” and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. When the study monitor visits the site, he or she will reconcile the drug accountability log with the products stored in the pharmacy.

### **10.6. Study Drug Handling and Disposal**

After receiving Sponsor approval in writing, the study center is responsible for returning all unused or partially used study drug to Sponsor or a designated third party or for preparing the study drug for destruction at the investigational study center.

## 11. PHARMACOKINETIC ASSESSMENTS

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 2](#).

### 11.1. Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling

For Part 1, blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [within 1 min prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 [within 1 min post-infusion], 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For Part 2, blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose). Participation in Part 2 of the study may extend beyond Day 22 if the amount of radioactivity found in the Day 22 urine or fecal samples is higher than 0.1% of the dose given. PK samples should continue to be collected every 7 days; the final PK draw should occur within  $\pm$  24 hours of the final urine or fecal sample (when both urine and fecal radioactivity is <0.1% of the dose given).

For Part 2, blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For the extension study, blood samples will be collected for PK analysis at the following times: Cycle 1/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).

The exact time that each sample is collected will be recorded by the study center, regardless of whether the sample is collected within the specified windows. A detailed description of the blood sample schedule and aliquot collection is included in [Table 8](#) and [Table 9](#) for Parts 1 and 2, respectively. Blood samples that will be used to measure the plasma concentration of [ $^{14}\text{C}$ ]-niraparib with accelerator mass spectrometry (AMS) in Part 1 will be transferred for analysis. Refer to the laboratory manual for further details on sample handling and shipping.

**Table 8: Part 1 Blood Sample Schedule and Aliquot Collection**

Day From Oral Dose	Time From Oral Dose	Time From Start of IV Infusion (hour)	Blood Samples for AMS Plasma Analysis of IV Dose (mL) <sup>a</sup>	Blood Samples for LC-MS/MS Plasma Analysis of Oral Dose (mL) <sup>b</sup>	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	—	2	2	8
	1 hr [ $\pm 2$ min]	—	—	2	2
	1.5 hr [ $\pm 2$ min]	—	—	2	2
	2 hr [within 1 min prior to IV infusion]	0 <sup>c</sup>	2	2	8
	2.125 hr [ $\pm 1$ min] <sup>d</sup>	0.125 <sup>c</sup>	2	—	4
	2.25 hr [within 1 min post-infusion] <sup>e</sup>	0.25 <sup>c</sup>	2	—	4
	2.33 hr [ $\pm 1$ min] <sup>f</sup>	0.33 <sup>c</sup>	2	—	4
	2.66 hr [ $\pm 1$ min] <sup>g</sup>	0.66 <sup>c</sup>	2	—	4
	3 hr [ $\pm 2$ min]	1 <sup>c</sup>	2	2	8
	4 hr [ $\pm 5$ min]	2 <sup>c</sup>	2	2	8
	6 hr [ $\pm 5$ min]	4 <sup>c</sup>	2	2	8
	12 hr [ $\pm 15$ min]	10 <sup>c</sup>	2	2	8
2	24 hr [ $\pm 1$ hr]	22 [ $\pm 1$ ]	2	2	8
3	48 hr [ $\pm 2$ hr]	46 [ $\pm 2$ ]	2	2	8
4	72 hr [ $\pm 4$ hr]	70 [ $\pm 4$ ]	2	2	8
5	96 hr [ $\pm 4$ hr]	94 [ $\pm 4$ ]	2	2	8
7	144 hr [ $\pm 4$ hr]	142 [ $\pm 4$ ]	2	2	8
9	192 hr [ $\pm 8$ hr]	190 [ $\pm 8$ ]	2	2	8
11	240 hr [ $\pm 12$ hr]	238 [ $\pm 12$ ]	2	2	8
13	288 hr [ $\pm 12$ hr]	286 [ $\pm 12$ ]	2	2	8
15	336 hr [ $\pm 12$ hr]	334 [ $\pm 12$ ]	2	2	8
22	504 hr [ $\pm 12$ hr]	502 [ $\pm 12$ ]	2	2	8

Abbreviations: AMS, accelerator mass spectrometry; IV, intravenous; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

<sup>a</sup> These samples will include 1 sample for AMS analysis (2 mL), and 1 sample that will be used as either a back-up sample for AMS analysis or potentially for LC-MS/MS analysis (2 mL).

<sup>b</sup> These samples will include 1 sample for LC-MS/MS analysis (2 mL) and 1 back-up sample (2 mL).

<sup>c</sup> Refer to Time From Oral Dose column for collection windows for the 0-10 hr Time From Start of IV Infusion.

<sup>d</sup> 2 hr 7.5 min

<sup>e</sup> 2 hr 15 min

<sup>f</sup> 2 hr 20 min

<sup>g</sup> 2 hr 40 min

**Table 9: Part 2 Blood Sample Schedule and Aliquot Collection**

Day	Time From Oral Dose	Blood Samples for LC-MS/MS Plasma Analysis <sup>a</sup> (mL)	Blood Sample for LSC Plasma Analysis (mL)	Blood Sample for LSC Whole Blood Analysis (mL)	Metabolite Profiling LC-MS/LC-MS/MS (mL)	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	2	2	2	2	10
	1 hr [±2 min]	2	2	2	2	10
	1.5 hr [±2 min]	2	2	2	—	8
	2 hr [±2 min]	2	2	2	2	10
	3 hr [±2 min]	2	2	2	2	10
	4 hr [±5 min]	2	2	2	—	8
	6 hr [±5 min]	2	2	2	2	10
	12 hr [± 15 min]	2	2	2	2	10
2	24 hr [±1 hr]	2	2	2	2	10
3	48 hr [±2 hr]	2	2	2	2	10
4	72 hr [±4 hr]	2	2	2	2	10
5	96 hr [±4 hr]	2	2	2	2	10
6	120 hr [±4 hr]	2	2	2	2	10
8	168 hr [±4 hr]	2	2	2	2	10
11	240 hr [±12 hr]	2	2	2	2	10
15	336 hr [±12 hr]	2	2	2	2	10
22	504 hr [±12 hr]	2	2	2	2	10

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> These samples will include 1 sample for analysis (2 mL), and 1 back-up sample (2 mL).

## 11.2. Urine Sample Collection

Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be

quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the urine sample schedule and the aliquot collection is included in Table 10. Refer to the laboratory manual for further details on sample storage conditions.

**Table 10: Urine Sample Schedule and Aliquot Collection**

Day	Interval (hour)	Niraparib Concentration LC-MS/MS Analysis (mL)	Radioactivity LSC Analysis (mL)	Metabolite Profiling LC-MS /LC-MS/MS (mL)	Total Urine Sample Volume (mL)
1	0 (predose)				
	0-12				
	12-24				
2	24-36				
	36-48				
3	48-72				
4	72-96				
5	96-120				
6	120-144				
7	144-168				
8	168-192				
9	192-216				
10	216-240				
11	240-264				
12	264-288				
13	288-312				
14	312-336				
15 <sup>a</sup>	336-360				

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be

collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

### 11.3. Fecal Sample Collection

Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the fecal sample schedule and the aliquot collection is included in Table 11. Refer to the laboratory manual for further details on sample storage conditions.

**Table 11: Fecal Sample Schedule and Aliquot Collection**

Day	Time (hour)	Aliquot Collection
1	0 (predose)	
	0-24	
2	24-48	
3	48-72	
4	72-96	
5	96-120	
6	120-144	Fecal samples will be processed per stool and analyzed in 24-hour intervals.
7	144-168	
8	168-192	Fecal samples will be homogenized with water (1:3, w/v). Several aliquots of 100 µL, 1 mL, and 10 mL (at least 3) will be saved for LSC analysis for radioactivity and metabolite profiling by LC-MS/MS.
9	192-216	
10	216-240	
11	240-264	
12	264-288	
13	288-312	
14	312-336	
15 <sup>a</sup>	336-360	

Abbreviation: LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be

collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

## 11.4. Sample Analysis

Analysis of blood, urine, and fecal samples includes the following:

- **Blood:** Blood samples will be analyzed for the plasma concentrations of niraparib and the major metabolite (M1) using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Part 1 blood samples will be analyzed for the plasma concentration of [<sup>14</sup>C]-niraparib using AMS. Part 2 blood samples will be analyzed for the whole blood and plasma concentrations of [<sup>14</sup>C]-niraparib using liquid scintillation counting (LSC). Part 2 plasma blood samples will be analyzed for metabolite profiling and identification using high resolution liquid chromatography-mass spectrometry (LC-MS), in combination with LC-MS/MS (including ion trap instruments). A quantitative LC-MS/MS method will be established for niraparib and the major carboxylic acid metabolite.
- **Urine:** Radioactivity content in urine samples will be determined by LSC. The concentration of niraparib and the major metabolite (M1) will be determined with LC-MS/MS. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).
- **Fecal:** Radioactivity content in fecal samples will be determined by LSC. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).

Pharmacokinetic parameters of interest include the following:

- **Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ; time to reach  $C_{max}$  ( $T_{max}$ ); and AUC from time 0 to the last quantifiable concentration ( $AUC_{0-last}$ ); and if the data allow: AUC from time 0 to infinity ( $AUC_{0-inf}$ ); apparent oral volume of distribution ( $Vd/F$ ); apparent oral clearance ( $CL/F$ ); and  $t_{1/2}$ . Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.
- **Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ ,  $Vd/F$ ,  $CL/F$ , and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$ (day), and total amount of drug excreted in the urine,  $A_e$ (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption ( $f$ ), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.

- **Extension study:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ , and  $t_{1/2}$ .

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## 12. ASSESSMENT OF SAFETY

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 2](#).

### 12.1. Safety Parameters

#### 12.1.1. Demographic and Baseline Characteristics

The following demographic information will be documented during the Screening Visit for Parts 1 and 2:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (Asian, Black, Caucasian, Other, Unknown)

The following baseline characteristics will be documented during the Screening Visit for Parts 1 and 2:

- History of drug, alcohol, or other substance abuse
- History of psychiatric illness
- Smoking history

#### 12.1.2. Medical History and Cancer History

Major medical history will be collected during the Screening Visit for Parts 1 and 2. Medical history will be obtained by interviewing the subjects or by reviewing their medical records.

Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis. CT scans should be performed per standard of care. If the subject discontinues due to disease progression, then the CT scan closest to the time of progression (EOT) should also be provided.

The following will be documented for cancer history:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Tumor grade
- Date of start of first treatment
- Agents used in first treatment
- Date of last dose of first treatment
- Date of relapse for each treatment

### **12.1.3. Prior and Concomitant Medications**

For prior medications, subjects will be asked during the Screening Visit for Parts 1 and 2 what medications they have taken during the last 30 days. All concomitant medications will be recorded from the time the subject signs the informed consent form (ICF) through completion of the study.

### **12.1.4. Vital Signs**

Blood pressure, pulse rate, and aural (tympanic) temperature will be measured while the subject is in the supine position at every visit that the subject is at the study center (see [Table 1](#), [Table 2](#), and [Table 3](#) for time points) after the subject has been resting for approximately 2 minutes. Vital signs will be collected prior to study drug administration on Day 1.

### **12.1.5. Weight, Height, and Body Mass Index**

Height (cm) and weight (kg) will be measured without shoes during the Screening Visit for Parts 1 and 2, and body mass index ( $\text{kg}/\text{m}^2$ ) will be calculated. For Parts 1 and 2, weight will also be measured at the Day 22 Visit. For the extension study, weight will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

### **12.1.6. Physical Examination**

The physical examination includes an assessment of general appearance and a review of body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems).

For Parts 1 and 2, the physical examination will be performed at the Screening Visit and at the Day 22 Visit. For the extension study, the physical examination will be performed at the Cycle 1/Day 1 Visit, Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

### **12.1.7. Electrocardiogram**

For Parts 1 and 2, the 12-lead ECG will be performed during the Screening Visit, the Day 1 Visit (predose and 2 hours postdose), the Day 22 Visit, and at EOT. For the Extension Study, the 12-lead ECG will be performed at Cycle 1 Day 1, at the Day 1 Visit (predose and 2 hours postdose) for each cycle during the extension study, and at EOT. Subjects will be in the supine position and resting for approximately 2 minutes before ECGs are recorded. For the measurement of QTc prolongation at the Screening Visit, results will include a mean of triplicate ECG readings (3 readings in rapid succession not more than 2 minutes apart).

### **12.1.8. Laboratory Assessments**

Laboratory assessments will be performed by the local laboratory at the study center. Blood samples should be drawn prior to study drug administration.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the study center. The Investigator or designee will indicate whether or not the value is of clinical significance and whether or not the subject requires intervention or further monitoring. Clinical significance will be defined as that requiring medical intervention. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality is found in the samples taken during the study, it should be recorded as an AE, and the subject will be followed until the test has normalized or stabilized.

#### **12.1.8.1. Parts 1 and 2 Laboratory Assessments**

Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio.

Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

Assessments will be conducted at the Screening Visit (must be collected within 72 hours prior to dosing), Day 15, and the Day 22 Visit.

For the hematology assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

#### **12.1.8.2. Extension Study Laboratory Assessments**

The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. The CBC will be conducted at the Screening Visit (drawn within 72 hours prior to study drug administration), Days 8, 15, and 22 of Cycle 1; Day 1 of every new cycle; and EOT.

Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. These assessments will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and EOT.

For the CBC, 3 mL of blood will be collected. For the coagulation assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **12.1.9. Laboratory Screenings**

#### **12.1.9.1. Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Screening**

Testing for HBV, HCV, and HIV will only be performed during the Screening Visit for Parts 1 and 2 if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

#### **12.1.9.2. Pregnancy Screen**

A serum pregnancy test will be performed for women of childbearing potential according to standard local procedures during the Screening Visit for Parts 1 and 2. All subjects who do not continue to the extension study will have a serum pregnancy test prior to study exit. Subjects who continue to the extension study will have a serum pregnancy test at the screening visit and at treatment discontinuation for the extension study. A urine pregnancy test will be performed every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.).

### **12.1.10. Eastern Cooperative Oncology Group Performance Scale**

The ECOG performance scale assesses the subject's general well-being and activities of daily life ([Appendix 20.2](#)). To be eligible for enrollment into this study, subjects must have an ECOG performance status of 0 to 2 during the Screening Visit for Parts 1 and 2. ECOG assessments will be conducted at the Parts 1 and 2/Day 22 Visit for subjects who are not enrolling in the extension study. The ECOG performance status will be reassessed during the extension study at the Screening Visit, the Day 1 Visit for Cycle 2 and each subsequent cycle, and at EOT. The same observer should assess performance status each time.

## **12.2. Adverse and Serious Adverse Events**

### **12.2.1. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be documented.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study treatment has been administered.

#### **12.2.1.2. Serious Adverse Event**

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:

- Results in death
  - This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)
  - An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

A distinction should be drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

### **12.2.1.3. Submission of Expedited Reports to Regulatory Authority, Sites, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

Per regulatory requirements, if an SAE report is required to be submitted to a Regulatory Authority a copy of this report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigators/site. TESARO or its designee will submit a copy of the report to their respective IRB or IEC.

### **12.3. Relationship to Study Drug**

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.
- Likely related: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.
- Unlikely to be related: A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.
- Unrelated: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

### **12.4. Recording Adverse Events**

AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see [Table 1](#), [Table 2](#), and [Table 3](#) for schedules of events). All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center.

Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the above SAE reporting process.

Abnormal laboratory values that constitute an AE or SAE must be collected. Investigators should assess the severity of AEs according to CTCAE ([HHS 2009](#)).

In general, CTCAE version 4.02 severity grades are the following:

- Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
- Grade 2: Moderate, minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under [Section 12.2.1.2](#). An AE of severe intensity may not be considered serious.

## 12.5. Reports of Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report notification form and reported to the Sponsor.

Pregnancies occurring in subjects enrolled in a study or in a female partner of a male subject must be reported and followed to outcome. The Investigator is responsible for documenting the course and outcome of any pregnancy that occurs while a subject is enrolled in the study and any pregnancy that occurs within 90 days after a subject's last dose.

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions.

Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death,

congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see [Section 12.6](#)).

The investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The Investigator should follow-up with the subject or the subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs after the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor, or designee, within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs.

#### PREGNANCY CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

#### 12.6. Reporting Adverse Events

The Investigator must report any SAE within 24 hours of becoming aware of the event. SAEs must be reported using the following contact information:

#### SAE REPORTING CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report Form must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant

and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the subject's personal identifiers (eg, subject name, medical record number) removed according to local regulations. The Investigator must sign and date all SAE forms.

*The minimum information required for an initial SAE report is:*

- Name of person sending the report (ie, name, address of Investigator)
- Subject identification (screening/randomization number, initials, NOT subject name)
- Protocol number
- Description of SAE
- Causality assessment

In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information.

## **13. STATISTICS**

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined in this section. Any deviations from the planned analyses will be described in the final integrated clinical study report.

### **13.1. General Considerations**

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum value, and maximum value). Categorical data will be summarized using counts and percentages. All data will be listed in data listings.

### **13.2. Study Population**

#### **13.2.1. Subject Disposition**

The number and percentage of subjects who enter and complete the study will be presented by group (ie, Part 1 subjects, Part 2 subjects, and extension study subjects). Subjects who fail to complete the study will be summarized and categorized by reason for termination (lost to follow-up, AE, etc.). In addition, the numbers of subjects in each analysis set will be summarized by group

#### **13.2.2. Demographic Information and Baseline Characteristics**

Demographics and baseline characteristics will be summarized descriptively by group and will be summarized for each of the defined analysis sets.

#### **13.2.3. Prior and Concomitant Medications**

Medications will be coded according to the current version of the World Health Organization Drug Dictionary. Prior and concomitant medications will be summarized descriptively by group.

#### **13.2.4. Protocol Deviations**

Protocol deviations will be listed by subject and a summary of significant protocol deviations by type will be produced.

#### **13.2.5. Analysis Populations**

**Safety Population:** All subjects who received study drug

**Pharmacokinetic Population:** All subjects who received study drug and provide adequate PK samples to calculate PK parameters

## **13.3. Safety Analyses**

### **13.3.1. Adverse Events**

AE terms will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing an event will be summarized

for each system organ class and preferred term by group. Likewise, AEs will also be tabulated according to intensity and relationship to study drug. Serious AEs, discontinuation due to AEs, and deaths will also be presented and listed separately, including the relationship to study drug.

### **13.3.2. Physical Examinations**

Physical examination findings will be summarized descriptively by group and by study visit. Individual data listings of physical examination findings will be presented for each subject.

### **13.3.3. Vital Signs**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for vital signs. Individual data listings of vital signs will be presented for each subject.

### **13.3.4. Electrocardiograms**

Observed values at baseline and changes from baseline will be summarized descriptively by group and study visit for the ECG parameters, including PR interval and QTc. Individual data listings of ECGs will be presented for each subject. Flags will be attached to QTc values of clinical significance. Individual data listings of clinically significant ECG parameters will also be presented for each subject.

### **13.3.5. Clinical Laboratory Assessments**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for the clinical laboratory results. Individual data listings of clinical laboratory results will be presented for each subject. Shift tables based on normal ranges will also be presented for select chemistry and hematology laboratory parameters. Flags will be attached to values outside of the laboratory's reference limits along with the PI's assessment of clinical significance. Clinically significant laboratory values will be summarized separately by group and study visit, and individual data listings of clinically significant laboratory results will also be presented for each subject.

## **13.4. Pharmacokinetic Analyses**

### **13.4.1. Part 1**

Plasma concentrations based on the radioactivity and mass spectrometry (MS) ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

### **13.4.2. Part 2**

Whole blood and plasma concentrations based on the radioactivity and MS ion intensity and, if appropriate, the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

### **13.4.3. Extension Study**

Plasma concentrations of niraparib based on MS ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics.

### **13.5. Determination of Sample Size**

The sample size of 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) is not based on statistical considerations and instead represents a balance between the number of subjects exposed and accounts for interindividual variability. Enrollment may be extended to replace subjects discontinued during the study ([Section 8.4.1](#)).

### **13.6. Data Monitoring**

An external Data Safety Monitoring Board will not be established for this study. The Sponsor will monitor safety throughout the project through the following efforts:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of nonserious AEs as they are recorded in the eCRF or appear in the source documents at the study center
- Periodic teleconferences with the PI to share experiences and ensure communication

Findings discovered to have immediate implication for the management of subjects on study treatment will be communicated to the PI in the timeframe associated with unexpected and drug-related SAEs.

Safety surveillance will include routine monitoring of clinical laboratory results, physical examination findings, vital signs, AE reporting, and ECG monitoring.

## 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

### 14.1. Study Monitoring

Before the study center can enter a subject into the study, a representative of the Sponsor or a designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or a representative will have regular contacts with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented in eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met the criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### 14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC, or an IRB may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

### **14.3. Ethics Committee**

The PI must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study, including the subject ICF and recruitment materials, must be maintained by the PI and made available for inspection.

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## **15. QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its representative may conduct a quality assurance audit. Refer to [Section 14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The PI must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### **16.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsor's policy on Bioethics.

### **16.3. Written Informed Consent**

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

The Sponsor or its representative will be allowed to conduct study center visits at the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **17.2. Retention of Records**

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **18. PUBLICATION POLICY**

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

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renseignements-cliniques.canada.ca/ci-rc/conditions

## 19. LIST OF REFERENCES

- Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245-51.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361(2):123-34.
- Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-61.
- Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res*. 2012;18(6):1726-34.
- Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-92.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
- Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19(5):1519-38.
- Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program*. 2007:172-8.
- TESARO, Inc. Niraparib. Investigator's brochure, Version 3.0. Waltham (MA); 2014. 115 p.
- Thompson JL and Crossman RR. Drug-induced QT prolongation. *US Pharm*. 2007;32(2):44-50.
- United States Department of Health and Human Services (HHS). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. 2009 [cited 30 Jan 2014]. Available from: [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE\\_4.02\\_2009-09-15\\_QuickReference\\_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf).
- United States Department of Health and Human Services (HHS), Food and Drug Administration, Center for Drug Evaluation and Research. Draft guidance. Drug interaction studies – Study design, data analysis, implications for dosing, and labeling recommendations. February 2012 [cited 04 Feb 2014]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>.

## 20. APPENDICES

### 20.1. Drugs Associated with QT Prolongation

Table 12: Drugs Associated with QT prolongation

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Itraconazole	Venlafaxine		Metoclopramide
	Azithromycin			Domperidone
				Ondansetron
				Diphenhydramine

Sources:

Thompson and Crossman, 2007

CredibleMeds web site. <https://www.crediblemeds.org>

US Pharmacist web site. Drug-induced QT prolongation page. Available at:

[http://www.uspharmacist.com/content/d/featured\\_articles/c/10396/](http://www.uspharmacist.com/content/d/featured_articles/c/10396/). Accessed 12 November 2013.

Cardiac Risk in the Young sponsored web site on Sudden Arrhythmic Death Syndrome. Available at:

[http://www.sads.org.uk/drugs\\_to\\_avoid.htm](http://www.sads.org.uk/drugs_to_avoid.htm). Accessed 24 October 2014.

## 20.2. Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Reference: [Oken et al, 1982](#)

1.

**TITLE PAGE**



**Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer**

**EudraCT No:** 2014-002011-41

**Sponsor:** TESARO, Inc.

1000 Winter Street, Suite 3300  
Waltham, MA 02451 USA

PI [REDACTED] MD, MPH  
Senior Medical Director

PI [REDACTED]  
PI [REDACTED], MD, PhD

PI [REDACTED], NL  
PI [REDACTED]  
PPD

Contract Research Organization:  
929 North Front Street  
Wilmington, NC 28401 USA

**Version of Protocol:** 2.1

**Original Final Protocol Date:** 28 May 2014

**Amendment 1:** 04 December 2014

This clinical investigation will be conducted according to this clinical protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki (Version 2008), and with other applicable regulatory requirements.

**Confidentiality Statement**

**All information contained in this document is privileged and confidential to TESARO. Any distribution, copying, or disclosure is strictly prohibited without prior written approval by TESARO.**

## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

### Declaration of the Principal Investigator

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Principal **PI** **estigator**

Name: **PI**  
Title: **Dr.**  
Institution: **PI**

Date  
**23-12-2014**

## SPONSOR SIGNATURE PAGE

### Declaration of Sponsor or Responsible Medical Expert

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

#### Sponsor Signatory

PI

PI

[PI ID]

Senior Medical Director  
TESARO, Inc.

04 Dec 2014

Date

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> TESARO, Inc.	
<b>Name of Investigational Product:</b> Niraparib	
<b>Name of Active Ingredient:</b> Niraparib	
<b>Title of Study:</b> Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer (Protocol Number PR-30-5015-C)	
<b>Study Center(s):</b> A single study center in the Netherlands	
<b>Principal Investigator:</b> PI, MD, PhD <b>Investigators:</b> Not applicable	
<b>Studied Period (years):</b> Estimated date first subject enrolled: February 2015 Estimated date last subject completed: December 2015	<b>Phase of Development:</b> 1
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"><li>To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer</li></ul> <b>Secondary:</b> <ul style="list-style-type: none"><li>To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer</li><li>To evaluate the safety and tolerability of niraparib in subjects with cancer</li></ul>	
<b>Methodology:</b> This is an open-label study with 2 parts, including an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP). <b>Part 1:</b> The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to	

the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu$ Ci of radioactivity ( $3 \times 100$ -mg capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu$ Ci of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. When subjects are not confined to the study center, urine and fecal samples will be collected via a courier service every 24 hours. For either the urine or fecal sample, if the total radioactivity in the Day 15 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, samples will continue to be collected every 24 hours on a weekly schedule.

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening. The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [ $3 \times 100$ -mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments and PK blood sampling. No fasting period is required during the extension study. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg ( $2 \times 100$ -mg capsules) QD and subsequently to 100 mg ( $1 \times 100$ -mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

**Number of Subjects (planned):**

**Part 1:** 6 subjects

**Part 2:** 6 subjects

Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

**Diagnosis and Main Criteria for Inclusion:**

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL} (5.6 \text{ mM})$
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
8. Subject is able to take oral medications.

**Exclusion Criteria:**

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered "controlled," the subject must have undergone treatment (eg, radiation or chemotherapy at least

- 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
4. Subject has known hypersensitivity to the components of niraparib.
  5. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
  6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
  7. Subject received a transfusion (platelets or red blood cells) within 4 weeks of study drug administration.
  8. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
  9. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
  10. Subject is immunocompromised with an active event and is being treated with medications.
  11. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
  12. Subject has a baseline corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.
  13. Subject is receiving concomitant medication(s) that prolong QTc ([Appendix 20.1](#)).
  14. Subject is starting chemotherapy within 3 weeks of study drug administration.
  15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
  16. Subject has a history of illicit drug use.
  17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
  18. Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of study drug administration.
  19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months or within 30 days prior to study drug administration for subjects participating in Parts 1 and 2, respectively.

**Investigational Product, Dosage and Mode of Administration:**

<p><b>Part 1:</b> Niraparib 300 mg (<math>3 \times 100</math>-mg capsules) orally and [<math>^{14}\text{C}</math>]-niraparib 100 <math>\mu\text{g}</math> (1 <math>\mu\text{Ci}</math> total radioactivity) intravenously</p> <p><b>Part 2:</b> [<math>^{14}\text{C}</math>]-niraparib 300 mg (<math>3 \times 100</math>-mg capsules; <math>3 \times 33.3 \mu\text{Ci}</math> radioactivity [100 <math>\mu\text{Ci}</math> total radioactivity]) orally</p> <p><b>Extension study:</b> Niraparib 300 mg (<math>3 \times 100</math>-mg capsules) orally</p>
<p><b>Duration of Treatment:</b></p> <p><b>Part 1:</b> Administration of a single oral dose, followed by a 15-minute IV infusion 2 hours after administration of the single oral dose</p> <p><b>Part 2:</b> Administration of a single oral dose</p> <p><b>Extension Study:</b> QD administration until treatment discontinuation</p>
<p><b>Reference Therapy, Dosage and Mode of Administration:</b></p> <p>None.</p>
<p><b>Criteria for Evaluation:</b></p> <p><b>Pharmacokinetics:</b></p> <p><b>Part 1:</b> Plasma niraparib concentrations will be used to determine the following PK parameters: maximum observed plasma concentration (<math>C_{\max}</math>); time to reach <math>C_{\max}</math> (<math>T_{\max}</math>); and area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration (<math>AUC_{0-\text{last}}</math>); and if the data allow: AUC from time 0 to infinity (<math>AUC_{0-\infty}</math>); apparent oral volume of distribution (<math>Vd/F</math>); apparent oral clearance (<math>CL/F</math>); and half-life (<math>t_{1/2}</math>). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.</p> <p><b>Part 2:</b> Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters: <math>C_{\max}</math>, <math>T_{\max}</math>, and <math>AUC_{0-\text{last}}</math>. The plasma niraparib concentration will be used to determine the following PK parameters: <math>C_{\max}</math>, <math>T_{\max}</math>, and <math>AUC_{0-\text{last}}</math>, and if the data allow: <math>AUC_{0-\infty}</math>, <math>Vd/F</math>, <math>CL/F</math>, and <math>t_{1/2}</math>. Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period, <math>A_e</math> (day), and total amount of drug excreted in the urine, <math>A_e</math> (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption (<math>f</math>), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.</p> <p><b>Extension Study:</b> Plasma niraparib concentrations will be used to determine the following PK parameters: <math>C_{\max}</math>, <math>T_{\max}</math>, <math>AUC_{0-\text{last}}</math>, <math>AUC_{0-\infty}</math>, and <math>t_{1/2}</math>.</p> <p><b>Safety:</b></p> <p>Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.</p>
<p><b>Statistical Methods:</b></p> <p><b>Pharmacokinetics:</b></p> <p>Whole blood (Part 2 only) and plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.</p> <p><b>Safety:</b></p> <p>All AEs will be listed and tabulated. Physical examination findings, vital signs, ECG parameters, and clinical laboratory results will be listed and summarized using descriptive statistics.</p>

**Table 1: Schedule of Assessments: Part 1**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X	X											X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>c</sup>	X												
Clinical laboratory assessments <sup>d</sup>	X	X											X
Serum pregnancy test (women of childbearing potential)	X												X <sup>e</sup>
Electrocardiogram (12-lead) <sup>f</sup>	X		X										X
ECOG performance status	X												X <sup>e</sup>
Confirm diagnosis with CT scan <sup>g</sup>	X												
Subject confinement		X <sup>h</sup>	X	X	X	X							
Niraparib oral administration <sup>i</sup>			X										

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
[ <sup>14</sup> C]-niraparib IV infusion <sup>j</sup>			X										
Pharmacokinetic blood sampling <sup>k</sup>			X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X <sup>e</sup>	

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous

<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>d</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>e</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see [Section 12.4](#)).

<sup>f</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>g</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>h</sup> If subject chooses to be admitted on Day -1.

<sup>i</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>j</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 (immediately after infusion), 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>l</sup> Serious adverse events (SAEs) will be recorded up to 30 days after EOT.

**Table 2: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent	X																
Subject demographics and baseline characteristics	X																
Medical history and cancer history	X																
Inclusion/exclusion criteria	X																
Physical examination	X																X
Height (cm)	X																
Weight (kg)	X	X															X
Body mass index (kg/m <sup>2</sup> )	X																
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X				X	X
HBV/HCV/HIV screening <sup>d</sup>	X																
Clinical laboratory assessments <sup>e</sup>	X	X														X	X
Serum pregnancy test (women of childbearing potential)	X																X <sup>f</sup>
Electrocardiogram (12-lead) <sup>g</sup>	X		X														X
ECOG performance status	X																X <sup>f</sup>
Confirm diagnosis with CT scan <sup>h</sup>	X																
Subject confinement		X <sup>i</sup>	X	X	X	X	X	X	X	X	X	X					
[ <sup>14</sup> C]-niraparib administration <sup>j</sup>			X														

Assessment or Procedure	Day Relative to First Dose of Study Drug															22 <sup>b</sup> End of Part 2
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Pharmacokinetic blood sampling <sup>k</sup>		X	X	X	X	X	X		X			X			X	X
Blood sample for metabolite profiling <sup>l</sup>		X	X	X	X	X	X		X			X			X	X
Urine collection <sup>m</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal collection <sup>n</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>o</sup>	X	X	X	X	X	X	X	X	X	X	X	X			X	X <sup>f</sup>

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote m and Footnote n), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>f</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see Section 12.4).

<sup>g</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>h</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>i</sup> If subject chooses to be admitted on Day -1.

<sup>j</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity (3 × 100-mg capsules, labeled active pharmaceutical ingredient [3 × 33.3 µCi of radioactivity]), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>l</sup> Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>m</sup> Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

<sup>n</sup> Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

<sup>o</sup> SAEs will be recorded up to 30 days after EOT.

**Table 3: Schedule of Assessments: Open-Label Extension Study**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c</sup>
		Day 1	Day 8	Day 15	Day 22		
Inclusion/exclusion criteria	X						
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>d</sup>	X		X	X	X	X	X
Complete blood count (CBC) <sup>e</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>f</sup>	X			X		X	X
Pregnancy test (women of childbearing potential) <sup>g</sup>	X					X	X
Study drug dispensed/collected <sup>h</sup>		X				X	X
Electrocardiogram (12-lead) <sup>i</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>j</sup>		X				X	X
Concomitant medication and AE monitoring <sup>k</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> Upon completion of Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening. The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2.

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days. Visits (except Cycle 1) will continue approximately every 4 weeks until treatment discontinuation

<sup>c</sup> The EOT visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria. If the subject discontinues due to disease progression, then the CT scan (taken per standard of care) closest to the time of progression (EOT) should be provided.

<sup>d</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.

<sup>e</sup> The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.

<sup>f</sup> Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.

<sup>g</sup> A serum pregnancy test will be conducted at the Screening Visit and at EOT. A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.).

<sup>h</sup> Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. No fasting period is required during the extension study. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. No new capsules will be dispensed at EOT.

<sup>i</sup> Subjects will have a 12-lead ECG at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at EOT.

<sup>j</sup> Blood samples for PK analysis will be collected at the following times: Cycle 1/Day 1 Visit (within 30 min predose and 2 hours ±15 min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours ±15 min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).

<sup>k</sup> SAEs will be recorded up to 30 days after EOT.

### 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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#### 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 4: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event
A <sub>e</sub> (day)	Amount of drug excreted in the urine in a 24-hour period
A <sub>e</sub> (total)	Total amount of drug excreted in the urine
ALT	Alanine aminotransferase
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC <sub>0-inf</sub>	Area under the plasma concentration-time curve from time 0 to infinity
AUC <sub>0-last</sub>	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
CA-125	Cancer antigen 125
CBC	Complete blood count
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent oral clearance
C <sub>max</sub>	Maximum observed plasma concentration
CNS	Central nervous system
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	Cytochrome P450 1A2
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
f	Extent of absorption
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HER2	Human epidermal growth factor 2
hERG	Human Ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HR	Homologous recombination
IBTs	Investigator's brochure
IC <sub>20</sub>	20% maximum inhibitory concentration
IC <sub>50</sub>	50% maximum inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LSC	Liquid scintillation counting
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
P-gp	P-glycoprotein
PARP	Poly (adenosine diphosphate-ribose) polymerase
PI	Principal Investigator
PK	Pharmacokinetic
QD	Once a day
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
t <sub>½</sub>	Half-life
TEAE	Treatment-emergent adverse event

Abbreviation or Specialist Term	Explanation
T <sub>max</sub>	Time to reach maximum observed plasma concentration
ULN	Upper limit of normal
Vd/F	Apparent oral volume of distribution

## 5. INTRODUCTION

### 5.1. Niraparib

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally active poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor with nanomolar potency that is being developed for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway or that are driven by PARP-mediated transcription factors.

#### 5.1.1. DNA Repair, Cancer, and PARP Inhibition

The PARP-1 and -2 enzymes, which are zinc-finger DNA-binding enzymes, play a crucial role in DNA repair. Upon formation of single-strand DNA breaks, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones, various DNA repair proteins, and PARP itself, which results in chromatin relaxation and fast recruitment of DNA repair factors that access and repair DNA breaks.

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of tumor cells than on normal cells. Therefore, a hypothesis is that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways.

Clinical studies have shown that PARP inhibitors have antitumor activity in certain types of cancer (Fong et al, 2009; Audeh et al, 2010; Gelmon et al, 2011; Kummar et al, 2012; Ledermann et al, 2012). Nonclinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with homozygous inactivation of either *BRCA-1* or *BRCA-2*; these breast cancer genes are known to be important in the HR DNA repair pathway. Germline mutations of *BRCA-1* and -2 are found in the majority of subjects with inherited breast or ovarian cancer. Inactivation of *BRCA-1* and -2 by mechanisms other than mutations, including somatic mutations and gene silencing by promoter hypermethylation, occurs in a significant portion of several sporadic cancers. In particular, for ovarian cancer, somatic *BRCA-1* or -2 mutations are found in 10% to 15% of all epithelial ovarian carcinomas, and strongly reduced expression of *BRCA-1* has been observed in a significant portion of sporadic ovarian cancers. Collectively, up to 40% to 60% of ovarian cancers might be responsive to PARP inhibitors as a consequence of defects in the BRCA-HR pathway, indicating a great potential for this approach in the therapy of ovarian cancer.

#### 5.1.2. Niraparib Nonclinical Studies

Niraparib inhibits normal DNA repair mechanisms and induces synthetic lethality when administered to cells with HR defects. In a *BRCA-1* mutant xenograft study in mice, niraparib dosed orally caused tumor regression, which was mirrored by a greater than 90% reduction in

tumor volume compared to control. In a *BRCA-2* mutant xenograft study in mice, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib was evaluated for its potential effects on cardiovascular and neurological function using several experimental safety pharmacology models. Niraparib inhibited the human Ether-à-go-go-related gene (hERG) current with a 50% maximal inhibitory concentration ( $IC_{50}$ ) value of 10  $\mu$ M and a 20% maximal inhibitory concentration ( $IC_{20}$ ) value of 3.8  $\mu$ M. Niraparib was administered intravenously during 3 sequential 30-minute periods at 1, 3, and 10 mg/kg to determine the effect of niraparib on cardiovascular function in 3 anesthetized dogs. Niraparib had no effect on the corrected QT interval (QTc; average plasma concentration  $\leq$ 15.3  $\mu$ M at 10 mg/kg). Mean arterial pressure and heart rate were increased at all doses evaluated, but the QRS cardiac interval was only increased at 10 mg/kg. Niraparib had no effect on neurological function in conscious mice at a single oral dose of 100 mg/kg.

The pharmacokinetics (PK) of niraparib in male Sprague-Dawley rats were determined following intravenous (IV; 3 mg/kg) and oral (5 mg/kg) administration. In male beagle dogs, PK studies were conducted following IV (1 mg/kg) and oral (3 mg/kg) administration. Following IV administration, niraparib demonstrated moderate-to-high clearance (28 and 31 mL/min/kg), a high volume of distribution (6.9 and 12.3 L/kg), and moderate terminal half-lives (3 and 6 hours) in rats and dogs, respectively. The oral bioavailability of niraparib was reasonable in both species (approximately 27% in rats and 57% in dogs).

Niraparib was investigated in 1-month oral toxicity studies in order to support daily dosing of the compound in humans, where niraparib was administered to rats and dogs by oral gavage once a day (QD) for up to 4 weeks followed by an approximately 2-week recovery period. Overall, nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. In the 1-month repeat-dose toxicity study in rats, mortality and physical signs were limited to the high dose (50 mg/kg/day). All changes observed at 50 mg/kg/day were resolved at the end of the 2-week recovery period or demonstrated reversibility, except for minimal treatment-related arterial hypertrophy in the heart and increased trabecula in the bone. At 10 mg/kg/day, there were no treatment-related changes other than increased urine volume in males. Based on these findings, the no observed adverse effect level (NOAEL) in the rat study was 10 mg/kg/day. The dose causing severe irreversible toxicity and death was 50 mg/kg/day. In the dog, decreases in hematology values were observed at a dose of 15 mg/kg/day, and all hematology changes seen during the dosing phase were resolved at the end of the recovery period. Although a decrease in amount of spermatogenic epithelium was observed after 1-month dosing at 6 mg/kg/day and 15 mg/kg/day and was not resolved at the end of the 2-week recovery period, the continued presence of spermatogenic epithelium supports that this change would eventually resolve. Therefore, based on these findings, the NOAEL for the dog study was 3 mg/kg/day.

The niraparib nonclinical studies are described in detail in the Investigator's Brochure (IB; version 3.0, 09 April 2014).

### **5.1.3. Niraparib Clinical Studies**

The niraparib clinical studies are described in detail in the IB (version 3.0, 09 April 2014).

### 5.1.3.1. Phase 1 Studies

Niraparib has been evaluated in a series of Phase 1 clinical studies in subjects with solid tumors. For these studies, niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide. As of 15 November 2013, 144 subjects have been treated with oral niraparib at doses up to 400 mg QD in Phase 1 studies, and treatment with niraparib has been generally well tolerated.

The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were (n=144): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), rash (10.4%), dizziness (9.7%), electrocardiogram (ECG) QT prolonged (9.7%), pyrexia (9.7%), abdominal distension (9.0%), urinary tract infection (9.0%), weight decreased (9.0%), abdominal pain lower (8.3%), alopecia (8.3%), neoplasm malignant (8.3%), dry mouth (7.6%), hypoalbuminemia (7.6%), musculoskeletal pain (7.6%), stomatitis (7.6%), arthralgia (6.9%), blood creatinine increase (6.9%), chills (6.9%), dyspepsia (6.9%), hypomagnesemia (6.9%), paresthesia (6.9%), aspartate aminotransferase (AST) increased (6.3%), dehydration (6.3%), musculoskeletal chest pain (6.3%), neck pain (6.3%), alanine aminotransferase (ALT) increased (5.6%), dysgeusia (5.6%), myalgia (5.6%), and palpitations (5.6%).

The most commonly reported drug-related (>5.0%) AEs (all grades) in the clinic were (n=129): fatigue (45.1%), nausea (42.4%), anemia (41.0%), thrombocytopenia (32.6%), decreased appetite (23.6%), neutropenia (22.2%), vomiting (22.2%), constipation (19.4%), leukopenia (18.1%), diarrhea (10.4%), insomnia (8.3%), dyspnea (6.9%), ECG QT prolonged (6.9%), headache (6.3%), stomatitis (6.3%), hyponatremia (5.6%), and alopecia (5.6%).

#### 5.1.3.1.1. Study PN001

The maximum tolerated dose (MTD) of niraparib dosed orally QD was determined to be 300 mg in subjects with advanced solid tumors or hematologic malignancies. The dose-limiting toxicity for niraparib is thrombocytopenia, with Grade 4 thrombocytopenia reported in 2 of 6 subjects treated at the 400-mg dose level. For the 44 subjects treated at the MTD, 21 subjects experienced thrombocytopenia, 16 subjects experienced neutropenia, and 34 subjects experienced anemia.

During routine safety monitoring, 12 of 104 subjects reported AEs of prolonged QTc (6 subjects experienced a Grade 1 event, 5 subjects experienced a Grade 2 event, and 1 subject experienced a Grade 3 event). Preliminary evaluation showed 8 of these subjects (7.7%) had QT prolongation that was assessed as at least possibly related to study drug. Of these 8 subjects, 7 received 300 mg of niraparib QD and 1 received 210 mg of niraparib QD. A total of 8 subjects exceeded a 30-msec change from baseline during the study, with the maximum being 70 msec. Given that these were spontaneous reports, and not part of a controlled QTc evaluation, it would be difficult to assess the relationship to niraparib. Until a more rigorous evaluation of QTc can be conducted, subjects should be evaluated for QTc prolongation.

A preliminary analysis of plasma drug concentration profiles indicated that the maximum observed plasma concentration ( $C_{max}$ ) after oral dosing occurred at approximately 3 hours. There was an approximate 3- to 4-fold accumulation in the area under the plasma concentration-time curve (AUC),  $C_{max}$ , and plasma concentration at 24 hours postdose from Cycle 1/Day 1 to Cycle 2/Day 1. Mean apparent terminal half-life ( $t_{1/2}$ ) ranged from 32.8 to 46.0 hours over the 60- to 400-mg dose range. PK parameters appeared to be dose-proportional.

Although efficacy was not the primary objective for this Phase 1 study, antitumor activity was observed in subjects taking niraparib as monotherapy at oral dose levels ranging from 60 to 400 mg. Based on Investigator evaluation using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or cancer antigen 125 (CA-125) criteria, an overall response rate of 13% was observed for all subjects in this study. Analysis of the 20 *BRCA* mutant ovarian cancer subjects enrolled in the study demonstrated that this group showed a 35% overall response rate according to RECIST version 1.1 and/or CA-125 criteria.

#### 5.1.3.2. Phase 3 Studies

The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline *BRCA* mutation breast cancer subjects (PR-30-5010-C; BRAVO) and to platinum-sensitive ovarian cancer subjects (PR-30-5011-C; NOVA). A total of 55 subjects had been randomized in the Phase 3 clinical study program as of 07 January 2014. Preliminary results from 15 subjects who completed the PR-30-5011-C study suggest administration of niraparib with food is expected to have a negligible effect on the PK of niraparib. Of the 16 subjects enrolled in the PR-30-5011-C study as of 15 November 2013, the most commonly reported AEs were gastrointestinal disorders (constipation, nausea, and vomiting) and metabolism and nutrition disorders (decreased appetite).

#### 5.1.4. Risks and Benefits

The potential benefit of niraparib treatment for patients with cancer is tumor regression.

Nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. The most commonly reported AEs in the clinic for the Phase 1 studies, where niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide, were (Section 5.1.3.1): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), and rash (10.4%). The Investigator should monitor subjects closely for these AEs.

As Phase 1 studies have shown that niraparib is safe and well tolerated, the potential benefits outweigh the potential risks.

When taking niraparib, caution should be used when also taking medications that are inducers of cytochrome P450 1A2 (CYP1A2) or inhibitors or inducers of P-glycoprotein (P-gp; Section 9.2).

The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs ([Section 9.2](#)).

## **5.2. Rationale for Current Study**

This is an open-label study with 2 parts, including an extension study following completion of Parts 1 or 2, that is being conducted in approximately 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) with cancer to examine the absorption, metabolism, excretion, and absolute bioavailability of niraparib. This study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

The oral bioavailability of niraparib has been determined in rats and dogs ([Section 5.1.2](#)), but has yet to be determined in human subjects, including those with cancer. Therefore, this study will examine the absolute oral bioavailability of niraparib and the absorption, metabolism, excretion, and mass balance of oral [ $^{14}\text{C}$ ]-niraparib in subjects with cancer.

The oral dose of niraparib used in this study is 300 mg, which is the MTD of niraparib ([Section 5.1.3.1.1](#)). A total of 144 subjects have been treated with niraparib up to 400 mg QD in Phase 1 studies, and the 300-mg daily dose of niraparib is considered safe and generally well tolerated (IB version 3.0, 09 April [2014](#)). The 300-mg daily dose of niraparib is currently being administered in 2 Phase 3 studies ([Section 5.1.3.2](#)).

This study will be the first-in-human administration of the IV formulation of niraparib. Data from the nonclinical studies did not demonstrate any safety issues that would preclude testing of IV niraparib in humans, and a microdose (100  $\mu\text{g}$ ) of niraparib is being administered in the current study.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Primary Objective**

- To determine the absolute bioavailability of niraparib by using an IV niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer.

### **6.2. Secondary Objectives**

- To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer.
- To evaluate the safety and tolerability of niraparib in subjects with cancer.

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is an open-label study with 2 parts, including an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with GCP.

**Part 1:** The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of  $100 \mu\text{g}$  niraparib, containing approximately  $1 \mu\text{Ci}$  of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and PK blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately  $100 \mu\text{Ci}$  of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu\text{Ci}$  of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. When subjects are not confined to the study center, urine and fecal samples will be collected via a courier service every 24 hours. For either the urine or fecal sample, if the total radioactivity in the Day 15 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 29. As long as the radioactivity remains

higher than 0.1% of the dose given, samples will continue to be collected every 24 hours on a weekly schedule.

**Extension study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening. The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) and will undergo safety assessments and PK blood sampling. (QD)No fasting period is required during the extension study. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

The schedule of assessments for Part 1, Part 2, and the extension study are presented in [Table 1](#), [Table 2](#) and [Table 3](#), respectively.

## 7.2. Number of Subjects

There will be 6 subjects in Part 1 of the study and 6 subjects in Part 2 of the study. Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects will be eligible to participate in the open-label extension study.

## 7.3. Treatment Assignment

At the Screening Visit, subjects will be offered the option to participate in either part of the study until 1 part of the study is fully enrolled, at which time subjects can only be screened for the remaining part of the study, or for future replacements ([Section 8.4.1](#)).

## 7.4. Dose Adjustment Criteria

During the extension study, dose interruption or reduction will be allowed based on treatment side effects. Treatment must be interrupted for any nonhematologic National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.02; [HHS 2009](#)) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days, the subject may restart treatment with niraparib, but with a dose level reduction according to Table 5 if prophylaxis is not considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted. Dose reductions for any CTCAE Grade 2 events that are bothersome to the subject will be permitted per the Investigator's judgment.

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 28-day dose interruption period, and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

**Table 5: Niraparib Dose Reductions for Nonhematologic Toxicities**

Event <sup>a</sup>	Dose <sup>b</sup>
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE $\geq$ 28 days	Discontinue study drug

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; QD, once a day; SAE, serious adverse event.

<sup>a</sup> Dose reductions for any NCI-CTCAE Grade 2 events that are bothersome to the subject will be permitted per the Investigator's judgment.

<sup>b</sup> Dose not to be decreased below 100 mg QD.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts, as outlined in Table 6.

**Table 6: Niraparib Dose Modification/Reduction for Hematologic Toxicities**

Event	Dose Modification
Platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq$ 100,000/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at the same dose or a reduced dose based on clinical judgment.

Event	Dose Modification
Second occurrence of platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count <75,000/ $\mu$ L*	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophils <1000/ $\mu$ L	Study drugs must be interrupted until neutrophil counts are $\geq 1500/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin <8 g/dL	Study drugs must be interrupted until hemoglobin is $\geq 9 \text{ g/dL}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviation: CBC, complete blood count.

\*For patients with a platelet count  $\leq 10,000/\mu\text{L}$ , a prophylactic platelet transfusion per guidelines may be considered (Schiffer et al., 2001; Slichter, 2007). For patients taking anticoagulation or antiplatelet drugs consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as  $\leq 20,000/\mu\text{L}$ .

If dose interruption or modification is required at any point on study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for CBC will be required for an additional 28 days after the AE has been resolved to the specified levels, after which monitoring every 28 days may resume. Weekly blood draws for CBC can be collected either at the study center or local laboratories. If the hematologic toxicity has not recovered to the specified levels within 28 days of the dose interruption period and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

For major surgery while on treatment, up to 28 days of drug interruption is allowed.

Once the dose of study drug has been reduced, any re-escalation must be discussed with the Medical Monitor.

All dose interruptions and reductions (including any missed doses) and the reasons for the interruptions and reductions will be recorded in the electronic case report form (eCRF).

## 7.5. Criteria for Study Termination

If in the opinion of the Investigator or Sponsor there is reasonable or sufficient cause, this study may be prematurely terminated at any time. Written notification documenting the reason for study termination will be provided to the Investigator or Sponsor by the terminating party. Circumstances that may warrant termination include study center performance issues, a potential new finding with the study drug, or changes in the development program. See [Section 8.4](#) for subject withdrawal criteria. Additional circumstances include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enroll subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of study drug

Should the study be stopped prematurely, all study materials must be returned to the Sponsor or be disposed of according to the Sponsor's specifications.

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## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a PARP inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL} (5.6 \text{ mM})$
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. AST and ALT  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
8. Subject is able to take oral medications.

### 8.2. Subject Exclusion Criteria

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS)

disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.

4. Subject has known hypersensitivity to the components of niraparib.
5. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
7. Subject received a transfusion (platelets or red blood cells) within 4 weeks of study drug administration.
8. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
9. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
10. Subject is immunocompromised with an active event and is being treated with medications.
11. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
12. Subject has a baseline QTc prolongation of >470 msec at the Screening Visit.
13. Subject is receiving concomitant medication(s) that prolong QTc ([Appendix 20.1](#)).
14. Subject is starting chemotherapy within 3 weeks of study drug administration.
15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
16. Subject has a history of illicit drug use.
17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
18. Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of study drug administration.

19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months or within 30 days prior to study drug administration for subjects participating in Parts 1 and 2, respectively.

### **8.3. Restrictions During Study**

Restrictions during the study include the following:

1. If sexually active, subjects of reproductive potential and their partners must agree to the use of 2 of the following highly effective forms of contraception throughout their participation in the study and for 90 days after the last dose of study drug:
  - Condom with spermicide and one of the following:
    - Oral contraceptive or hormonal therapy (eg, hormone implants)
    - Placement of an intrauterine device

Acceptable nonhormonal birth control methods include the following:

- Total sexual abstinence
- Vasectomized sexual partner and use of a male condom, with subject assurance that partner received postvasectomy confirmation of azoospermia
- Tubal occlusion and use of a male condom with spermicide
- Intrauterine device and use of a male condom with spermicide

Acceptable hormonal methods with use of a male condom with spermicide include the following:

- Etonogestrel implants (eg, Implanon®, Norplant®)
- Normal and low dose combined oral pills
- Norelgestromin/ethynodiol dihydrogesterone transdermal system.
- Intravaginal device (eg, ethynodiol dihydrogesterone and etonogestrel)
- Cerazette® (desogestrel), which is currently the only highly efficacious progesterone-based pill

2. No other anticancer therapy is permitted during the course of study treatment for any subject. If the subject discontinues study drug, this restriction no longer applies. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.
3. Prophylactic cytokine (granulocyte colony-stimulating factor) administration should not be given in the first cycle of the extension study but may be administered in subsequent cycles according to local guidelines.
4. An increased risk of infection with the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are

unknown, so live virus and bacterial vaccines should not be administered to subjects in the study.

5. Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to receiving study drug and/or within 6 hours after receiving study drug.
6. Subjects who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.
7. Subjects should try to minimize their exposure to ultraviolet light, including natural or artificial sunlight (tanning beds or ultraviolet A or B treatment), while taking niraparib to avoid any possibility of phototoxicity. If subjects need to be outdoors while taking niraparib, they should wear loose fitting clothes and hats that protect skin from direct sun exposure and discuss other sun protection measures with their physician, such as ultraviolet-protection sunscreen. If a sunburn-like reaction or skin eruption occurs, subjects should contact their physician.

#### **8.4. Subject Withdrawal Criteria**

A subject may be discontinued from treatment or from the study for the following reasons:

- AE
  - For the extension study only, a treatment-related CTCAE Grade 3 or 4 AE that has not reverted to CTCAE Grade 1 or less within 28 days. At the Investigator's discretion, following dose interruption (no longer than 28 days), subjects may be considered for dose reductions ([Section 7.4](#)), providing they have not already undergone the maximum number of 2 dose reductions allowed. If a CTCAE Grade 3 or 4 AE recurs upon rechallenging with study drug at the lowest allowable dose, the subject must permanently discontinue treatment.
- Unacceptable toxicity
  - For the extension study only, if the subject experiences a dose interruption or modification because of a hematologic toxicity and the platelet count has not reverted to  $\geq 100,000/\mu\text{L}$  within 28 days, the subject should be discontinued.
- Severe noncompliance with the protocol, as judged by the Investigator and/or Sponsor.
- Subject becomes pregnant
- It is in the best interest of the subject, as judged by the Investigator and/or Sponsor
- Subject withdraws consent
- Sponsor decision to terminate study
- For the extension study only, disease progression and/or clinical criteria per standard of care

Subjects who discontinue from treatment will continue to receive follow-up safety assessments (see [Section 12](#)) as part of the study for 30 days from the last dose, unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the subject, who is at any time and for any reason free to discontinue their participation in the study, without prejudice to further treatment
- Death
- Loss to follow-up

If a subject is lost to follow-up or withdraws from study treatment, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.

#### **8.4.1. Replacement of Subjects**

After consultation between the Sponsor and the Principal Investigator (PI), enrollment may be extended to replace subject(s) discontinued during the study. Replacement subjects will be assigned the next available dosing number for the part of study in which the discontinued subjects were enrolled.

## 9. TREATMENT OF SUBJECTS

### 9.1. Description of Study Drug

The investigational products that will be used in this study are summarized in Table 7.

**Table 7: Investigational Product**

	Investigational Product		
<b>Product Name</b>	niraparib	[ <sup>14</sup> C]-niraparib IV solution	[ <sup>14</sup> C]-niraparib
<b>Dosage Form</b>	100-mg capsules	sterile solution for IV administration	capsules
<b>Unit Dose</b>	300 mg (3 × 100-mg capsules)	100 µg (1 µCi total radioactivity)	300 mg (3 × 100-mg capsules, 3 x 33.3 µCi of radioactivity [100 µCi total radioactivity])
<b>Route of Administration</b>	oral	IV	oral
<b>Study Phase Taken</b>	Part 1 and Extension	Part 1	Part 2

Abbreviation: IV, intravenous.

### 9.2. Prior and Concomitant Medications

Any medication the subject takes during the study other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication.

All prior and concomitant medications will be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Known prior medications that exclude a subject from participating in the study are described in the Exclusion Criteria ([Section 8.2](#)). Prohibited concomitant medications are described in [Section 8.3](#). Additionally, niraparib has potential to induce CYP1A2. Therefore, subjects should be advised to use caution when taking medications that are also inducers of CYP1A2. Examples of CYP1A2 inducers include montelukast, phenytoin, moricizine, omeprazole, and phenobarbital ([HHS 2012](#)). Niraparib is a substrate for P-gp; therefore, subjects should be advised to use caution when taking medications that are inhibitors or inducers of P-gp. Examples of P-gp inhibitors include the following ([HHS 2012](#)): amiodarone, azithromycin, captoril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and

verapamil. Examples of P-gp inducers include the following ([HHS 2012](#)): avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir-ritonavir.

The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs.

### **9.3. Treatment Compliance**

The study staff will maintain an ongoing record of the dispensing and administration of study drug for each subject. For the extension study, subjects will be instructed to return any unused study drug to the study center during their visit on the first day of each cycle or at EOT. Drug accountability will be performed on capsules dispensed versus returned to the study center at each visit and the number of days since the last visit.

### **9.4. Randomization and Blinding**

Subjects will not be randomly assigned and instead may choose in which part of the study to participate ([Section 7.3](#)). This is an unblinded study.

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Study Drug**

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor.

### **10.2. Study Drug Packaging and Labeling**

Niraparib 100-mg capsules (unlabeled active pharmaceutical ingredient) will be packed in high-density polyethylene bottles with child-resistant closures. Each dosing container will contain a sufficient number of capsules for 1 treatment cycle. Niraparib will be dispensed to subjects on Day 1 of every cycle of the extension study.

The IV solution and oral capsules will be prepared for dosing by Quotient Clinical from [<sup>14</sup>C]-niraparib active pharmaceutical ingredient following Good Manufacturing Practices. Information on the preparation, packaging, and labeling of the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity per 300-mg dose) of niraparib can be found in the investigational medicinal product dossier.

### **10.3. Study Drug Storage**

The 100-mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 15°C to 25°C. Until study drug is dispensed to the subjects, the study drug will be stored in a suitable container, at storage conditions specified by the Sponsor, in a securely locked area, accessible to authorized personnel only.

Information for storing the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity) of niraparib can be found in the investigational medicinal product dossier.

### **10.4. Study Drug Administration**

For Part 1, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For Part 2, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3\text{ }\mu\text{Ci}$  of radioactivity]), on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Subjects will continue fasting until

4 hours after administration of study drug, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For the extension study, 300 mg of niraparib ( $3 \times 100\text{-mg}$  capsules, unlabeled active pharmaceutical ingredient) will be administered orally QD until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)); dose interruptions and reductions will be allowed based on treatment side effects ([Section 7.4](#)). No fasting period is required during the extension study. Subjects will be instructed to take the niraparib dose at the same time of day, preferably in the morning. The first dose will be administered at the study center. Subjects must swallow and not chew the capsules, and the consumption of water is permissible.

## **10.5. Study Drug Accountability**

The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes the subject number, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as “returned” and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. When the study monitor visits the site, he or she will reconcile the drug accountability log with the products stored in the pharmacy.

## **10.6. Study Drug Handling and Disposal**

After receiving Sponsor approval in writing, the study center is responsible for returning all unused or partially used study drug to Sponsor or a designated third party or for preparing the study drug for destruction at the investigational study center.

## 11. PHARMACOKINETIC ASSESSMENTS

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 2](#).

### 11.1. Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling

For Part 1, blood samples for PK analysis will be collected at the following times: predose (0 hour within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 (immediately after infusion), 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For the extension study, blood samples will be collected for PK analysis at the following times: Cycle 1/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).

The exact time that each sample is collected will be recorded by the study center, regardless of whether the sample is collected within the specified windows. A detailed description of the blood sample schedule and aliquot collection is included in [Table 8](#) and [Table 9](#) for Parts 1 and 2, respectively. Blood samples that will be used to measure the plasma concentration of [ $^{14}\text{C}$ ]-niraparib with accelerator mass spectrometry (AMS) in Part 1 will be transferred for analysis. Refer to the laboratory manual for further details on sample handling and shipping.

**Table 8: Part 1 Blood Sample Schedule and Aliquot Collection**

Day From Oral Dose	Time From Oral Dose	Time From Start of IV Infusion (hour)	Blood Samples for AMS Plasma Analysis of IV Dose (mL) <sup>a</sup>	Blood Samples for LC-MS/MS Plasma Analysis of Oral Dose (mL) <sup>b</sup>	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	—	2	2	8
	1 hr [±2 min]	—	—	2	2
	1.5 hr [±2 min]	—	—	2	2
	2 hr [prior to IV infusion]	0 (predose)	2	2	8
	2.125 hr [±1 min]	0.125	2	—	4
	2.25 hr [immediately after infusion]	0.25	2	—	4
	2.33 hr [±1 min]	0.33	2	—	4
	2.66 hr [±1 min]	0.66	2	—	4
	3 hr [±2 min]	1	2	2	8
	4 hr [±5 min]	2	2	2	8
	6 hr [±5 min]	4	2	2	8
	12 hr [± 15 min]	10 [±1]	2	2	8
2	24 hr [±1 hr]	22 [±1]	2	2	8
3	48 hr [±2 hr]	46 [±2]	2	2	8
4	72 hr [±4 hr]	70 [±4]	2	2	8
5	96 hr [±4 hr]	94 [±4]	2	2	8
7	144 hr [±4 hr]	142 [±4]	2	2	8
9	192 hr [±8 hr]	190 [±8]	2	2	8
11	240 hr [±12 hr]	238 [±12]	2	2	8
13	288 hr [±12 hr]	286 [±12]	2	2	8
15	336 hr [±12 hr]	334 [±12]	2	2	8
22	504 hr [±12 hr]	502 [±12]	2	2	8

Abbreviations: AMS, accelerator mass spectrometry; IV, intravenous; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

<sup>a</sup> These samples will include 1 sample for immediate AMS analysis (2 mL), and 1 sample that will be used as either a back-up sample for AMS analysis or potentially for LC-MS/MS analysis (2 mL).

<sup>b</sup> These samples will include 1 sample for immediate analysis (2 mL) and 1 back-up sample (2 mL).

**Table 9: Part 2 Blood Sample Schedule and Aliquot Collection**

Day	Time From Oral Dose	Blood Samples for LC-MS/MS Plasma Analysis <sup>a</sup> (mL)		Blood Sample for LSC Plasma Analysis (mL)	Blood Sample for LSC Whole Blood Analysis (mL)	Metabolite Profiling LC-MS/LC-MS/MS (mL)	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	2	2	2	2	2	10
	1 hr [ $\pm 2$ min]	2	2	2	2	2	10
	1.5 hr [ $\pm 2$ min]	2	2	2	2	—	8
	2 hr [ $\pm 2$ min]	2	2	2	2	2	10
	3 hr [ $\pm 2$ min]	2	2	2	2	2	10
	4 hr [ $\pm 5$ min]	2	2	2	2	—	8
	6 hr [ $\pm 5$ min]	2	2	2	2	2	10
	12 hr [ $\pm 15$ min]	2	2	2	2	2	10
2	24 hr [ $\pm 1$ hr]	2	2	2	2	2	10
3	48 hr [ $\pm 2$ hr]	2	2	2	2	2	10
4	72 hr [ $\pm 4$ hr]	2	2	2	2	2	10
5	96 hr [ $\pm 4$ hr]	2	2	2	2	2	10
6	120 hr [ $\pm 4$ hr]	2	2	2	2	2	10
8	168 hr [ $\pm 4$ hr]	2	2	2	2	2	10
11	240 hr [ $\pm 12$ hr]	2	2	2	2	2	10
15	336 hr [ $\pm 12$ hr]	2	2	2	2	2	10
22	504 hr [ $\pm 12$ hr]	2	2	2	2	2	10

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> These samples will include 1 sample for immediate analysis (2 mL), and 1 back-up sample (2 mL).

## 11.2. Urine Sample Collection

Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples

will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the urine sample schedule and the aliquot collection is included in Table 10. Refer to the laboratory manual for further details on sample storage conditions.

**Table 10: Urine Sample Schedule and Aliquot Collection**

Day	Interval (hour)	Niraparib Concentration LC-MS/MS Analysis (mL)	Radioactivity LSC Analysis (mL)	Metabolite Profiling LC-MS /LC-MS/MS (mL)	Total Urine Sample Volume (mL)
1	0 (predose)	2 × 3	1	3 × 10	37
	0-12				
	12-24				
2	24-36	2 × 3	1	3 × 10	37
	36-48				
3	48-72				
4	72-96				
5	96-120				
6	120-144				
7	144-168				
8	168-192				
9	192-216				
10	216-240				
11	240-264				
12	264-288				
13	288-312				
14	312-336				
15 <sup>a</sup>	336-360				

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

### 11.3. Fecal Sample Collection

Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the fecal sample schedule and the aliquot collection is included in Table 11. Refer to the laboratory manual for further details on sample storage conditions.

**Table 11: Fecal Sample Schedule and Aliquot Collection**

Day	Time (hour)	Aliquot Collection
1	0 (predose)	
	0-24	
2	24-48	
3	48-72	
4	72-96	
5	96-120	
6	120-144	
7	144-168	
8	168-192	
9	192-216	
10	216-240	
11	240-264	
12	264-288	
13	288-312	
14	312-336	
15 <sup>a</sup>	336-360	

Abbreviation: LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

## 11.4. Sample Analysis

Analysis of blood, urine, and fecal samples includes the following:

- **Blood:** Blood samples will be analyzed for the plasma concentration of niraparib using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Part 1 blood samples will be analyzed for the plasma concentration of [<sup>14</sup>C]-niraparib using AMS. Part 2 blood samples will be analyzed for the whole blood and plasma concentrations of [<sup>14</sup>C]-niraparib using liquid scintillation counting (LSC). Part 2 plasma blood samples will be analyzed for metabolite profiling and identification using high resolution liquid chromatography-mass spectrometry (LC-MS), in combination with LC-MS/MS (including ion trap instruments). A quantitative LC-MS/MS method will be established for niraparib and the major carboxylic acid metabolite.
- **Urine:** Radioactivity content in urine samples will be determined by LSC. The concentration of niraparib will be determined with LC-MS/MS. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).
- **Fecal:** Radioactivity content in fecal samples will be determined by LSC. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).

Pharmacokinetic parameters of interest include the following:

- **Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ; time to reach  $C_{max}$  ( $T_{max}$ ); and AUC from time 0 to the last quantifiable concentration ( $AUC_{0-last}$ ); and if the data allow: AUC from time 0 to infinity ( $AUC_{0-inf}$ ); apparent oral volume of distribution (Vd/F); apparent oral clearance (CL/F); and  $t_{1/2}$ . Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.
- **Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ , Vd/F, CL/F, and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$  (day), and total amount of drug excreted in the urine,  $A_e$  (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption (f), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.
- **Extension study:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ , and  $t_{1/2}$ .

## 12. ASSESSMENT OF SAFETY

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 7.1](#).

### 12.1. Safety Parameters

#### 12.1.1. Demographic and Baseline Characteristics

The following demographic information will be documented during the Screening Visit for Parts 1 and 2:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (Asian, Black, Caucasian, Other, Unknown)

The following baseline characteristics will be documented during the Screening Visit for Parts 1 and 2:

- History of drug, alcohol, or other substance abuse
- History of psychiatric illness
- Smoking history

#### 12.1.2. Medical History and Cancer History

Major medical history will be collected during the Screening Visit for Parts 1 and 2. Medical history will be obtained by interviewing the subjects or by reviewing their medical records.

Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis. CT scans should be performed per standard of care. If the subject discontinues due to disease progression, then the CT scan closest to the time of progression (EOT) should also be provided.

The following will be documented for cancer history:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Date of start of first treatment
- Agents used in first treatment
- Date of last dose of first treatment
- Dates of start of all subsequent treatments

- Agents used in all subsequent treatments
- Dates of last dose of all subsequent treatments
- Date of recurrence for each treatment

#### **12.1.3. Prior and Concomitant Medications**

For prior medications, subjects will be asked during the Screening Visit for Parts 1 and 2 what medications they have taken during the last 30 days. All concomitant medications will be recorded from the time the subject signs the informed consent form (ICF) through completion of the study.

#### **12.1.4. Vital Signs**

Blood pressure, pulse rate, and aural (tympanic) temperature will be measured while the subject is in the supine position at every visit that the subject is at the study center (see [Table 1](#), [Table 2](#), and [Table 3](#) for time points) after the subject has been resting for approximately 2 minutes. Vital signs will be collected prior to study drug administration on Day 1.

#### **12.1.5. Weight, Height, and Body Mass Index**

Height (cm) and weight (kg) will be measured without shoes during the Screening Visit for Parts 1 and 2, and body mass index ( $\text{kg}/\text{m}^2$ ) will be calculated. For Parts 1 and 2, weight will also be measured at the Day -1 Visit and the Day 22 Visit. For the extension study, weight will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

#### **12.1.6. Physical Examination**

The physical examination includes an assessment of general appearance and a review of body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems).

For Parts 1 and 2, the physical examination will be performed at the Screening Visit and at the Day 22 Visit. For the extension study, the physical examination will be performed at the Cycle 1/Day 1 Visit, Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

#### **12.1.7. Electrocardiogram**

The 12-lead ECG will be performed during the Screening Visit for Parts 1 and 2, the Day 1 Visit (predose and 2 hours postdose) for Parts 1 and 2, the Day 22 Visit for Parts 1 and 2, the Day 1 Visit (predose and 2 hours postdose) for each cycle during the extension study, and at EOT. Subjects will be in the supine position and resting for approximately 2 minutes before ECGs are recorded. For the measurement of QTc prolongation at the Screening Visit, results will include a mean of triplicate ECG readings (3 readings in rapid succession not more than 2 minutes apart).

### **12.1.8. Laboratory Assessments**

Laboratory assessments will be performed by the local laboratory at the study center. Blood samples should be drawn prior to study drug administration.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the study center. The Investigator or designee will indicate whether or not the value is of clinical significance and whether or not the subject requires intervention or further monitoring. Clinical significance will be defined as that requiring medical intervention. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality is found in the samples taken during the study, it should be recorded as an AE, and the subject will be followed until the test has normalized or stabilized.

#### **12.1.8.1. Parts 1 and 2 Laboratory Assessments**

Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio.

Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

Assessments will be conducted at the Screening Visit, the Day -1 Visit, and Day 22 Visit for Part 1; and the Day -1, 15, and 22 Visits for Part 2.

For the hematology assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

#### **12.1.8.2. Extension Study Laboratory Assessments**

The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. The CBC will be conducted at the Screening Visit, Day 1 (only if the Screening Visit and Cycle 1/Day 1 Visit occur on the same day [ie, CBC does not need to be conducted at the Screening Visit and again at Day 1 Visit]) Days 8, 15, and 22 of Cycle 1; Day 1 of every new cycle; and EOT.

Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. These assessments will be measured at the Screening Visit, Day 1 (only if the Screening Visit and Cycle 1/Day 1 Visit occur on the same day [ie, coagulation assessments do not need to be conducted at the Screening Visit and again at Day 1 Visit]), the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and EOT.

If the laboratory assessments for the Screening Visit are performed on the same day as the Cycle 1/Day 1 Visit, the results will be reviewed prior to dosing.

For the CBC, 3 mL of blood will be collected. For the coagulation assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **12.1.9. Laboratory Screenings**

#### **12.1.9.1. Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Screening**

Testing for HBV, HCV, and HIV will only be performed during the Screening Visit for Parts 1 and 2 if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

#### **12.1.9.2. Pregnancy Screen**

A serum pregnancy test will be performed for women of childbearing potential according to standard local procedures during the Screening Visit for Parts 1 and 2. All subjects who do not continue to the extension study will have a serum pregnancy test prior to study exit. Subjects who continue to the extension study will have a serum pregnancy test at the screening visit and at treatment discontinuation for the extension study. A urine pregnancy test will be performed during the Screening Visit for the extension study and every 3 months thereafter (Cycle 4, Cycle 7, etc.).

### **12.1.10. Eastern Cooperative Oncology Group Performance Scale**

The ECOG performance scale assesses the subject's general well-being and activities of daily life ([Appendix 20.2](#)). To be eligible for enrollment into this study, subjects must have an ECOG performance status of 0 to 2 during the Screening Visit for Parts 1 and 2. ECOG assessments will be conducted at the Parts 1 and 2/Day 22 Visit for subjects who are not enrolling in the extension study. The ECOG performance status will be reassessed during the extension study at the Screening Visit, the Day 1 Visit for Cycle 2 and each subsequent cycle, and at EOT. The same observer should assess performance status each time.

## **12.2. Adverse and Serious Adverse Events**

### **12.2.1. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be documented.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study treatment has been administered.

#### **12.2.1.2. Serious Adverse Event**

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:

- Results in death
  - This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)
  - An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

A distinction should be drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

### **12.2.1.3. Submission of Expedited Reports to Regulatory Authority, Sites, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

Per regulatory requirements, if an SAE report is required to be submitted to a Regulatory Authority a copy of this report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigators/site. TESARO or its designee will submit a copy of the report to their respective IRB or IEC.

## **12.3. Relationship to Study Drug**

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.
- Likely related: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.
- Unlikely to be related: A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.
- Unrelated: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

## **12.4. Recording Adverse Events**

AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see [Table 1](#), [Table 2](#), and [Table 3](#) for schedules of events). All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center.

Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the above SAE reporting process.

Abnormal laboratory values that constitute an AE or SAE must be collected. Investigators should assess the severity of AEs according to CTCAE ([HHS 2009](#)).

In general, CTCAE version 4.02 severity grades are the following:

- Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under [Section 12.2.1.2](#). An AE of severe intensity may not be considered serious.

## 12.5. Reports of Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report notification form and reported to the Sponsor.

Pregnancies occurring in subjects enrolled in a study or in a female partner of a male subject must be reported and followed to outcome. The Investigator is responsible for documenting the course and outcome of any pregnancy that occurs while a subject is enrolled in the study and any pregnancy that occurs within 90 days after a subject's last dose.

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death,

congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see [Section 12.6](#)).

The investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The Investigator should follow-up with the subject or the subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs after the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor, or designee, within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs.

#### PREGNANCY CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

#### 12.6. Reporting Adverse Events

The Investigator must report any SAE once he/she becomes aware of within 24 hours of becoming aware of the event. SAEs must be reported using the following contact information:

#### SAE REPORTING CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report Form must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant

and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the subject's personal identifiers (eg, subject name, medical record number) removed according to local regulations. The Investigator must sign and date all SAE forms.

*The minimum information required for an initial SAE report is:*

- Name of person sending the report (ie, name, address of Investigator)
- Subject identification (screening/randomization number, initials, NOT subject name)
- Protocol number
- Description of SAE
- Causality assessment

In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information.

## **13. STATISTICS**

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined in this section. Any deviations from the planned analyses will be described in the final integrated clinical study report.

### **13.1. General Considerations**

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum value, and maximum value). Categorical data will be summarized using counts and percentages. All data will be listed in data listings.

### **13.2. Study Population**

#### **13.2.1. Subject Disposition**

The number and percentage of subjects who enter and complete the study will be presented by group (ie, Part 1 subjects, Part 2 subjects, and extension study subjects). Subjects who fail to complete the study will be summarized and categorized by reason for termination (lost to follow-up, AE, etc.). In addition, the numbers of subjects in each analysis set will be summarized by group

#### **13.2.2. Demographic Information and Baseline Characteristics**

Demographics and baseline characteristics will be summarized descriptively by group and will be summarized for each of the defined analysis sets.

#### **13.2.3. Prior and Concomitant Medications**

Medications will be coded according to the current version of the World Health Organization Drug Dictionary. Prior and concomitant medications will be summarized descriptively by group.

#### **13.2.4. Protocol Deviations**

Protocol deviations will be listed by subject and a summary of significant protocol deviations by type will be produced.

#### **13.2.5. Analysis Populations**

**Safety Population:** All subjects who received study drug

**Pharmacokinetic Population:** All subjects who received study drug and provide adequate PK samples to calculate PK parameters

## **13.3. Safety Analyses**

### **13.3.1. Adverse Events**

AE terms will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing an event will be summarized

for each system organ class and preferred term by group. Likewise, AEs will also be tabulated according to intensity and relationship to study drug. Serious AEs, discontinuation due to AEs, and deaths will also be presented and listed separately, including the relationship to study drug.

### **13.3.2. Physical Examinations**

Physical examination findings will be summarized descriptively by group and by study visit. Individual data listings of physical examination findings will be presented for each subject.

### **13.3.3. Vital Signs**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for vital signs. Individual data listings of vital signs will be presented for each subject. Flags will be attached to values outside of the reference limits along with the PI's assessment of clinical significance. Clinically significant vital signs will be summarized separately by group and study visit, and individual data listings of clinically significant vital signs will also be presented for each subject.

### **13.3.4. Electrocardiograms**

Observed values at baseline and changes from baseline will be summarized descriptively by group and study visit for the ECG parameters, including PR interval and QTc. Individual data listings of ECGs will be presented for each subject. Flags will be attached to QTc values of clinical significance. Clinically significant ECG parameters will be summarized separately by group, and individual data listings of clinically significant ECG parameters will also be presented for each subject.

### **13.3.5. Clinical Laboratory Assessments**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for the clinical laboratory results. Individual data listings of clinical laboratory results will be presented for each subject. Shift tables will also be presented for select chemistry and hematology laboratory parameters. Flags will be attached to values outside of the laboratory's reference limits along with the PI's assessment of clinical significance. Clinically significant laboratory values will be summarized separately by group and study visit, and individual data listings of clinically significant laboratory results will also be presented for each subject.

## **13.4. Pharmacokinetic Analyses**

### **13.4.1. Part 1**

Plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

#### **13.4.2. Part 2**

Whole blood and plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

#### **13.4.3. Extension Study**

Plasma concentrations of niraparib based on mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics.

### **13.5. Determination of Sample Size**

The sample size of 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) is not based on statistical considerations and instead represents a balance between the number of subjects exposed and accounts for interindividual variability. Enrollment may be extended to replace subjects discontinued during the study ([Section 8.4.1](#)).

### **13.6. Data Monitoring**

An external Data Safety Monitoring Board will not be established for this study. The Sponsor will monitor safety throughout the project through the following efforts:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of nonserious AEs as they are recorded in the eCRF or appear in the source documents at the study center
- Periodic teleconferences with the PI to share experiences and ensure communication

Findings discovered to have immediate implication for the management of subjects on study treatment will be communicated to the PI in the timeframe associated with unexpected and drug-related SAEs.

Safety surveillance will include routine monitoring of clinical laboratory results, physical examination findings, vital signs, AE reporting, and ECG monitoring.

## 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

### 14.1. Study Monitoring

Before the study center can enter a subject into the study, a representative of the Sponsor or a designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or a representative will have regular contacts with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented in eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met the criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### 14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC, or an IRB may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

### **14.3. Ethics Committee**

The PI must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study, including the subject ICF and recruitment materials, must be maintained by the PI and made available for inspection.

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## **15. QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its representative may conduct a quality assurance audit. Refer to [Section 14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The PI must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### **16.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsor's policy on Bioethics.

### **16.3. Written Informed Consent**

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

The Sponsor or its representative will be allowed to conduct study center visits at the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **17.2. Retention of Records**

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **18. PUBLICATION POLICY**

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

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renseignements-cliniques.canada.ca/ci-rc/conditions

## 19. LIST OF REFERENCES

- Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245-51.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361(2):123-34.
- Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-61.
- Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res*. 2012;18(6):1726-34.
- Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-92.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
- Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19(5):1519-38.
- Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program*. 2007:172-8.
- TESARO, Inc. Niraparib. Investigator's brochure, Version 3.0. Waltham (MA); 2014. 115 p.
- Thompson JL and Crossman RR. Drug-induced QT prolongation. *US Pharm*. 2007;32(2):44-50.
- United States Department of Health and Human Services (HHS). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. 2009 [cited 30 Jan 2014]. Available from: [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE\\_4.02\\_2009-09-15\\_QuickReference\\_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf).
- United States Department of Health and Human Services (HHS), Food and Drug Administration, Center for Drug Evaluation and Research. Draft guidance. Drug interaction studies – Study design, data analysis, implications for dosing, and labeling recommendations. February 2012 [cited 04 Feb 2014]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>.

## 20. APPENDICES

### 20.1. Drugs Associated with QT Prolongation

Table 12: Drugs Associated with QT prolongation

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Itraconazole	Venlafaxine		Metoclopramide
	Azithromycin			Domperidone
				Ondansetron
				Diphenhydramine

Sources:

Thompson and Crossman, 2007

CredibleMeds web site. <https://www.crediblemeds.org>

US Pharmacist web site. Drug-induced QT prolongation page. Available at:

[http://www.uspharmacist.com/content/d/featured\\_articles/c/10396/](http://www.uspharmacist.com/content/d/featured_articles/c/10396/). Accessed 12 November 2013.

Cardiac Risk in the Young sponsored web site on Sudden Arrhythmic Death Syndrome. Available at:

[http://www.sads.org.uk/drugs\\_to\\_avoid.htm](http://www.sads.org.uk/drugs_to_avoid.htm). Accessed 24 October 2014.

## 20.2. Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Reference: [Oken et al, 1982](#)

**1.**

**TITLE PAGE**



**Absorption, Metabolism, Excretion, and the Determination of Absolute  
Bioavailability of Niraparib in Subjects with Cancer**

**EudraCT No:** 2014-002011-41

**Sponsor:** TESARO, Inc.

1000 Winter Street, Suite 3300  
Waltham, MA 02451 USA

PI [REDACTED] MD, MPH  
Senior Medical Director

PI [REDACTED]  
PI [REDACTED], MD, PhD

PI [REDACTED], NL  
PI PPD

**TESARO Medical Monitor:**

**Contract Research Organization:**

**Version of Protocol:**

**Original Final Protocol Date:**

**Amendment 1:** 01 December 2014

929 North Front Street  
Wilmington, NC 28401 USA

2.0

28 May 2014

This clinical investigation will be conducted according to this clinical protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki (Version 2008), and with other applicable regulatory requirements.

**Confidentiality Statement**

**All information contained in this document is privileged and confidential to TESARO. Any distribution, copying, or disclosure is strictly prohibited without prior written approval by TESARO.**

## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

### Declaration of the Principal Investigator

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

#### Principal Investigator

---

Name:

Title:

Institution:

---

Date

## SPONSOR SIGNATURE PAGE

### Declaration of Sponsor or Responsible Medical Expert

**Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

### Sponsor Signatory

PI

PI

PI D

Senior Medical Director  
TESARO, Inc.

03 Dec 2014

Date

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> TESARO, Inc.	
<b>Name of Investigational Product:</b> Niraparib	
<b>Name of Active Ingredient:</b> Niraparib	
<b>Title of Study:</b> Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer (Protocol Number PR-30-5015-C)	
<b>Study Center(s):</b> A single study center in the Netherlands	
<b>Principal Investigator:</b> PI, MD, PhD <b>Investigators:</b> Not applicable	
<b>Studied Period (years):</b> Estimated date first subject enrolled: February 2015 Estimated date last subject completed: December 2015	<b>Phase of Development:</b> 1
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"><li>To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer</li></ul> <b>Secondary:</b> <ul style="list-style-type: none"><li>To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer</li><li>To evaluate the safety and tolerability of niraparib in subjects with cancer</li></ul>	
<b>Methodology:</b> This is an open-label study with 2 parts, including an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP). <b>Part 1:</b> The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to	

the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu$ Ci of radioactivity ( $3 \times 100$ -mg capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu$ Ci of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. When subjects are not confined to the study center, urine and fecal samples will be collected via a courier service every 24 hours. For either the urine or fecal sample, if the total radioactivity in the Day 15 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, samples will continue to be collected every 24 hours on a weekly schedule.

**Extension Study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). Subjects have 7 days to complete the screening assessments. The Screening Visit should occur between 1 and 7 days after the last dose of study drug (Part 1 or Part 2). The Cycle 1/Day 1 Visit can occur on the same day as the Screening Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [ $3 \times 100$ -mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments and PK blood sampling. No fasting period is required during the extension study. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg ( $2 \times 100$ -mg capsules) QD and subsequently to 100 mg ( $1 \times 100$ -mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over Study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or

Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

**Number of Subjects (planned):**

**Part 1:** 6 subjects

**Part 2:** 6 subjects

Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects may be eligible to participate in the open-label extension study.

**Diagnosis and Main Criteria for Inclusion:**

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL} (5.6 \text{ mM})$
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
8. Subject is able to take oral medications.

**Exclusion Criteria:**

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered "controlled," the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must

have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.

4. Subject has known hypersensitivity to the components of niraparib.
5. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
7. Subject received a transfusion (platelets or red blood cells) within 4 weeks of study drug administration.
8. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
9. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
10. Subject is immunocompromised with an active event and is being treated with medications.
11. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
12. Subject has a baseline corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.
13. Subject is receiving concomitant medication(s) that prolong QTc ([Appendix 20.1](#)).
14. Subject is starting chemotherapy within 3 weeks of study drug administration.
15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
16. Subject has a history of illicit drug use.
17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
18. Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of study drug administration.
19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months or within 30 days prior to study drug administration for subjects participating in Parts 1 and 2, respectively.

**Investigational Product, Dosage and Mode of Administration:**

**Part 1:** Niraparib 300 mg (3 × 100-mg capsules) orally and [<sup>14</sup>C]-niraparib 100 µg (1 µCi total)

radioactivity) intravenously  
**Part 2:** [<sup>14</sup>C]-niraparib 300 mg (3 x 100-mg capsules; 3 x 33.3 µCi radioactivity [100 µCi total radioactivity]) orally  
**Extension study:** Niraparib 300 mg (3 × 100-mg capsules) orally

**Duration of Treatment:**

**Part 1:** Administration of a single oral dose, followed by a 15-minute IV infusion 2 hours after administration of the single oral dose

**Part 2:** Administration of a single oral dose

**Extension Study:** QD administration until treatment discontinuation

**Reference Therapy, Dosage and Mode of Administration:**

None.

**Criteria for Evaluation:**

**Pharmacokinetics:**

**Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters: maximum observed plasma concentration ( $C_{max}$ ); time to reach  $C_{max}$  ( $T_{max}$ ); and area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration ( $AUC_{0-last}$ ); and if the data allow: AUC from time 0 to infinity ( $AUC_{0-inf}$ ); apparent oral volume of distribution (Vd/F); apparent oral clearance (CL/F); and half-life ( $t_{1/2}$ ). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

**Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ , Vd/F, CL/F, and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$  (day), and total amount of drug excreted in the urine,  $A_e$  (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption (f), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.

**Extension Study:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ , and  $t_{1/2}$ .

**Safety:**

Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.

**Statistical Methods:**

**Pharmacokinetics:**

Whole blood (Part 2 only) and plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

**Safety:**

All AEs will be listed and tabulated. Physical examination findings, vital signs, ECG parameters, and clinical laboratory results will be listed and summarized using descriptive statistics.

**Table 1: Schedule of Assessments: Part 1**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X	X											X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>c</sup>	X												
Clinical laboratory assessments <sup>d</sup>	X	X											X
Serum pregnancy test (women of childbearing potential)	X												X <sup>e</sup>
Electrocardiogram (12-lead) <sup>f</sup>	X		X										X
ECOG performance status	X												X <sup>e</sup>
Confirm diagnosis with CT scan <sup>g</sup>	X												
Subject confinement		X <sup>h</sup>	X	X	X	X							
Niraparib oral administration <sup>i</sup>			X										
[ <sup>14</sup> C]-niraparib IV infusion <sup>j</sup>			X										

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Pharmacokinetic blood sampling <sup>k</sup>			X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>e</sup>

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous

<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>d</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>e</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see [Section 12.4](#)).

<sup>f</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>g</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>h</sup> If subject chooses to be admitted on Day -1.

<sup>i</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>j</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour within 30 min prior to dose), Day 1 (1 [±2 min], 1.5 [±2 min], 2 [prior to IV infusion], 2.125 [±1 min], 2.25 (immediately after infusion), 2.33 [±1 min], 2.66 [±1 min], 3 [±2 min], 4 [±5 min], 6 [±5 min], and 12 hours [±15 min] postdose), Day 2 (24 [±1] hours postdose), Day 3 (48 [±2] hours postdose), Day 4 (72 [±4] hours postdose), Day 5 (96 [±4] hours postdose), Day 7 (144 [±4] hours postdose), Day 9 (192 [±8] hours postdose), Day 11 (240 [±12] hours postdose), Day 13 (288 [±12] hours postdose), Day 15 (336 [±12] hours postdose), and Day 22 (504 [±12] hours postdose).

<sup>l</sup> Serious adverse events (SAEs) will be recorded up to 30 days after EOT.

**Table 2: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																	
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup> End of Part 2
Informed consent	X																	
Subject demographics and baseline characteristics	X																	
Medical history and cancer history	X																	
Inclusion/exclusion criteria	X																	
Physical examination	X																	X
Height (cm)	X																	
Weight (kg)	X	X																X
Body mass index (kg/m <sup>2</sup> )	X																	
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X					X	X
HBV/HCV/HIV screening <sup>d</sup>	X																	
Clinical laboratory assessments <sup>e</sup>	X	X															X	X
Serum pregnancy test (women of childbearing potential)	X																	X <sup>f</sup>
Electrocardiogram (12-lead) <sup>g</sup>	X		X															X
ECOG performance status	X																	X <sup>f</sup>
Confirm diagnosis with CT scan <sup>h</sup>	X																	
Subject confinement		X <sup>i</sup>	X	X	X	X	X	X	X	X	X	X						
[ <sup>14</sup> C]-niraparib administration <sup>j</sup>			X															

Assessment or Procedure	Day Relative to First Dose of Study Drug															22 <sup>b</sup> End of Part 2
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Pharmacokinetic blood sampling <sup>k</sup>		X	X	X	X	X	X		X			X			X	X
Blood sample for metabolite profiling <sup>l</sup>		X	X	X	X	X	X		X			X			X	X
Urine collection <sup>m</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal collection <sup>n</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>o</sup>	X	X	X	X	X	X	X	X	X	X	X	X			X	X <sup>f</sup>

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote m and Footnote n), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>f</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see Section 12.4).

<sup>g</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>h</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>i</sup> If subject chooses to be admitted on Day -1.

<sup>j</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity (3 × 100-mg capsules, labeled active pharmaceutical ingredient [3 × 33.3 µCi of radioactivity]), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>l</sup> Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<sup>m</sup> Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

<sup>n</sup> Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

<sup>o</sup> SAEs will be recorded up to 30 days after EOT.

**Table 3: Schedule of Assessments: Open-Label Extension Study**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c</sup>
		Day 1	Day 8	Day 15	Day 22		
Inclusion/exclusion criteria	X						
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>d</sup>	X		X	X	X	X	X
Complete blood count (CBC) <sup>e</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>f</sup>	X			X		X	X
Pregnancy test (women of childbearing potential) <sup>g</sup>	X					X	X
Study drug dispensed/collected <sup>h</sup>		X				X	X
Electrocardiogram (12-lead) <sup>i</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>j</sup>		X				X	X
Concomitant medication and AE monitoring <sup>k</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> Upon completion of Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in Table 6. Subjects have 7 days to complete the screening assessments. The Screening Visit should occur within 1 and 7 days after the last dose of study drug (Part 1 or Part 2). The Cycle 1/Day 1 Visit can occur on the same day as the Screening Visit.

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days. Visits (except Cycle 1) will continue approximately every 4 weeks until treatment discontinuation

<sup>c</sup> The EOT visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria. If the subject discontinues due to disease progression, then the CT scan (taken per standard of care) closest to the time of progression (EOT) should be provided.

<sup>d</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.

<sup>e</sup> The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.

<sup>f</sup> Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.

<sup>g</sup> A serum pregnancy test will be conducted at the Screening Visit and at EOT. A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.).

<sup>h</sup> Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. No fasting period is required during the extension study. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. No new capsules will be dispensed at EOT.

<sup>i</sup> Subjects will have a 12-lead ECG at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at EOT.

<sup>j</sup> Blood samples for PK analysis will be collected at the following times: Cycle 1/Day 1 Visit (within 30 min predose and 2 hours ±15 min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours ±15 min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).

<sup>k</sup> SAEs will be recorded up to 30 days after EOT.

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#### 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 4: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event
A <sub>e</sub> (day)	Amount of drug excreted in the urine in a 24-hour period
A <sub>e</sub> (total)	Total amount of drug excreted in the urine
ALT	Alanine aminotransferase
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC <sub>0-inf</sub>	Area under the plasma concentration-time curve from time 0 to infinity
AUC <sub>0-last</sub>	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
CA-125	Cancer antigen 125
CBC	Complete blood count
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent oral clearance
C <sub>max</sub>	Maximum observed plasma concentration
CNS	Central nervous system
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	Cytochrome P450 1A2
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
f	Extent of absorption
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HER2	Human epidermal growth factor 2
hERG	Human Ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HR	Homologous recombination
IBTs	Investigator's brochure
IC <sub>20</sub>	20% maximum inhibitory concentration
IC <sub>50</sub>	50% maximum inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LSC	Liquid scintillation counting
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
P-gp	P-glycoprotein
PARP	Poly (adenosine diphosphate-ribose) polymerase
PI	Principal Investigator
PK	Pharmacokinetic
QD	Once a day
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
t <sub>½</sub>	Half-life
TEAE	Treatment-emergent adverse event

Abbreviation or Specialist Term	Explanation
T <sub>max</sub>	Time to reach maximum observed plasma concentration
ULN	Upper limit of normal
Vd/F	Apparent oral volume of distribution

## 5. INTRODUCTION

### 5.1. Niraparib

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally active poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor with nanomolar potency that is being developed for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway or that are driven by PARP-mediated transcription factors.

#### 5.1.1. DNA Repair, Cancer, and PARP Inhibition

The PARP-1 and -2 enzymes, which are zinc-finger DNA-binding enzymes, play a crucial role in DNA repair. Upon formation of single-strand DNA breaks, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones, various DNA repair proteins, and PARP itself, which results in chromatin relaxation and fast recruitment of DNA repair factors that access and repair DNA breaks.

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of tumor cells than on normal cells. Therefore, a hypothesis is that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways.

Clinical studies have shown that PARP inhibitors have antitumor activity in certain types of cancer (Fong et al, 2009; Audeh et al, 2010; Gelmon et al, 2011; Kummar et al, 2012; Ledermann et al, 2012). Nonclinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with homozygous inactivation of either *BRCA-1* or *BRCA-2*; these breast cancer genes are known to be important in the HR DNA repair pathway. Germline mutations of *BRCA-1* and -2 are found in the majority of subjects with inherited breast or ovarian cancer. Inactivation of *BRCA-1* and -2 by mechanisms other than mutations, including somatic mutations and gene silencing by promoter hypermethylation, occurs in a significant portion of several sporadic cancers. In particular, for ovarian cancer, somatic *BRCA-1* or -2 mutations are found in 10% to 15% of all epithelial ovarian carcinomas, and strongly reduced expression of *BRCA-1* has been observed in a significant portion of sporadic ovarian cancers. Collectively, up to 40% to 60% of ovarian cancers might be responsive to PARP inhibitors as a consequence of defects in the BRCA-HR pathway, indicating a great potential for this approach in the therapy of ovarian cancer.

#### 5.1.2. Niraparib Nonclinical Studies

Niraparib inhibits normal DNA repair mechanisms and induces synthetic lethality when administered to cells with HR defects. In a *BRCA-1* mutant xenograft study in mice, niraparib dosed orally caused tumor regression, which was mirrored by a greater than 90% reduction in

tumor volume compared to control. In a *BRCA-2* mutant xenograft study in mice, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib was evaluated for its potential effects on cardiovascular and neurological function using several experimental safety pharmacology models. Niraparib inhibited the human Ether-à-go-go-related gene (hERG) current with a 50% maximal inhibitory concentration ( $IC_{50}$ ) value of 10  $\mu$ M and a 20% maximal inhibitory concentration ( $IC_{20}$ ) value of 3.8  $\mu$ M. Niraparib was administered intravenously during 3 sequential 30-minute periods at 1, 3, and 10 mg/kg to determine the effect of niraparib on cardiovascular function in 3 anesthetized dogs. Niraparib had no effect on the corrected QT interval (QTc; average plasma concentration  $\leq$ 15.3  $\mu$ M at 10 mg/kg). Mean arterial pressure and heart rate were increased at all doses evaluated, but the QRS cardiac interval was only increased at 10 mg/kg. Niraparib had no effect on neurological function in conscious mice at a single oral dose of 100 mg/kg.

The pharmacokinetics (PK) of niraparib in male Sprague-Dawley rats were determined following intravenous (IV; 3 mg/kg) and oral (5 mg/kg) administration. In male beagle dogs, PK studies were conducted following IV (1 mg/kg) and oral (3 mg/kg) administration. Following IV administration, niraparib demonstrated moderate-to-high clearance (28 and 31 mL/min/kg), a high volume of distribution (6.9 and 12.3 L/kg), and moderate terminal half-lives (3 and 6 hours) in rats and dogs, respectively. The oral bioavailability of niraparib was reasonable in both species (approximately 27% in rats and 57% in dogs).

Niraparib was investigated in 1-month oral toxicity studies in order to support daily dosing of the compound in humans, where niraparib was administered to rats and dogs by oral gavage once a day (QD) for up to 4 weeks followed by an approximately 2-week recovery period. Overall, nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. In the 1-month repeat-dose toxicity study in rats, mortality and physical signs were limited to the high dose (50 mg/kg/day). All changes observed at 50 mg/kg/day were resolved at the end of the 2-week recovery period or demonstrated reversibility, except for minimal treatment-related arterial hypertrophy in the heart and increased trabecula in the bone. At 10 mg/kg/day, there were no treatment-related changes other than increased urine volume in males. Based on these findings, the no observed adverse effect level (NOAEL) in the rat study was 10 mg/kg/day. The dose causing severe irreversible toxicity and death was 50 mg/kg/day. In the dog, decreases in hematology values were observed at a dose of 15 mg/kg/day, and all hematology changes seen during the dosing phase were resolved at the end of the recovery period. Although a decrease in amount of spermatogenic epithelium was observed after 1-month dosing at 6 mg/kg/day and 15 mg/kg/day and was not resolved at the end of the 2-week recovery period, the continued presence of spermatogenic epithelium supports that this change would eventually resolve. Therefore, based on these findings, the NOAEL for the dog study was 3 mg/kg/day.

The niraparib nonclinical studies are described in detail in the Investigator's Brochure (IB; version 3.0, 09 April 2014).

### 5.1.3. Niraparib Clinical Studies

The niraparib clinical studies are described in detail in the IB (version 3.0, 09 April 2014).

### 5.1.3.1. Phase 1 Studies

Niraparib has been evaluated in a series of Phase 1 clinical studies in subjects with solid tumors. For these studies, niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide. As of 15 November 2013, 144 subjects have been treated with oral niraparib at doses up to 400 mg QD in Phase 1 studies, and treatment with niraparib has been generally well tolerated.

The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were (n=144): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), rash (10.4%), dizziness (9.7%), electrocardiogram (ECG) QT prolonged (9.7%), pyrexia (9.7%), abdominal distension (9.0%), urinary tract infection (9.0%), weight decreased (9.0%), abdominal pain lower (8.3%), alopecia (8.3%), neoplasm malignant (8.3%), dry mouth (7.6%), hypoalbuminemia (7.6%), musculoskeletal pain (7.6%), stomatitis (7.6%), arthralgia (6.9%), blood creatinine increase (6.9%), chills (6.9%), dyspepsia (6.9%), hypomagnesemia (6.9%), paresthesia (6.9%), aspartate aminotransferase (AST) increased (6.3%), dehydration (6.3%), musculoskeletal chest pain (6.3%), neck pain (6.3%), alanine aminotransferase (ALT) increased (5.6%), dysgeusia (5.6%), myalgia (5.6%), and palpitations (5.6%).

The most commonly reported drug-related (>5.0%) AEs (all grades) in the clinic were (n=129): fatigue (45.1%), nausea (42.4%), anemia (41.0%), thrombocytopenia (32.6%), decreased appetite (23.6%), neutropenia (22.2%), vomiting (22.2%), constipation (19.4%), leukopenia (18.1%), diarrhea (10.4%), insomnia (8.3%), dyspnea (6.9%), ECG QT prolonged (6.9%), headache (6.3%), stomatitis (6.3%), hyponatremia (5.6%), and alopecia (5.6%).

#### 5.1.3.1.1. Study PN001

The maximum tolerated dose (MTD) of niraparib dosed orally QD was determined to be 300 mg in subjects with advanced solid tumors or hematologic malignancies. The dose-limiting toxicity for niraparib is thrombocytopenia, with Grade 4 thrombocytopenia reported in 2 of 6 subjects treated at the 400-mg dose level. For the 44 subjects treated at the MTD, 21 subjects experienced thrombocytopenia, 16 subjects experienced neutropenia, and 34 subjects experienced anemia.

During routine safety monitoring, 12 of 104 subjects reported AEs of prolonged QTc (6 subjects experienced a Grade 1 event, 5 subjects experienced a Grade 2 event, and 1 subject experienced a Grade 3 event). Preliminary evaluation showed 8 of these subjects (7.7%) had QT prolongation that was assessed as at least possibly related to study drug. Of these 8 subjects, 7 received 300 mg of niraparib QD and 1 received 210 mg of niraparib QD. A total of 8 subjects exceeded a 30-msec change from baseline during the study, with the maximum being 70 msec. Given that these were spontaneous reports, and not part of a controlled QTc evaluation, it would be difficult to assess the relationship to niraparib. Until a more rigorous evaluation of QTc can be conducted, subjects should be evaluated for QTc prolongation.

A preliminary analysis of plasma drug concentration profiles indicated that the maximum observed plasma concentration ( $C_{max}$ ) after oral dosing occurred at approximately 3 hours. There was an approximate 3- to 4-fold accumulation in the area under the plasma concentration-time curve (AUC),  $C_{max}$ , and plasma concentration at 24 hours postdose from Cycle 1/Day 1 to Cycle 2/Day 1. Mean apparent terminal half-life ( $t_{1/2}$ ) ranged from 32.8 to 46.0 hours over the 60- to 400-mg dose range. PK parameters appeared to be dose-proportional.

Although efficacy was not the primary objective for this Phase 1 study, antitumor activity was observed in subjects taking niraparib as monotherapy at oral dose levels ranging from 60 to 400 mg. Based on Investigator evaluation using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or cancer antigen 125 (CA-125) criteria, an overall response rate of 13% was observed for all subjects in this study. Analysis of the 20 *BRCA* mutant ovarian cancer subjects enrolled in the study demonstrated that this group showed a 35% overall response rate according to RECIST version 1.1 and/or CA-125 criteria.

#### **5.1.3.2. Phase 3 Studies**

The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline *BRCA* mutation breast cancer subjects (PR-30-5010-C; BRAVO) and to platinum-sensitive ovarian cancer subjects (PR-30-5011-C; NOVA). A total of 55 subjects had been randomized in the Phase 3 clinical study program as of 07 January 2014. Preliminary results from 15 subjects who completed the PR-30-5011-C study suggest administration of niraparib with food is expected to have a negligible effect on the PK of niraparib. Of the 16 subjects enrolled in the PR-30-5011-C study as of 15 November 2013, the most commonly reported AEs were gastrointestinal disorders (constipation, nausea, and vomiting) and metabolism and nutrition disorders (decreased appetite).

#### **5.1.4. Risks and Benefits**

The potential benefit of niraparib treatment for patients with cancer is tumor regression.

Nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. The most commonly reported AEs in the clinic for the Phase 1 studies, where niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide, were (Section 5.1.3.1): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), and rash (10.4%). The Investigator should monitor subjects closely for these AEs.

As Phase 1 studies have shown that niraparib is safe and well tolerated, the potential benefits outweigh the potential risks.

When taking niraparib, caution should be used when also taking medications that are inducers of cytochrome P450 1A2 (CYP1A2) or inhibitors or inducers of P-glycoprotein (P-gp; Section 9.2).

## 5.2. Rationale for Current Study

This is an open-label study with 2 parts, including an extension study following completion of Parts 1 or 2, that is being conducted in approximately 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) with cancer to examine the absorption, metabolism, excretion, and absolute bioavailability of niraparib. This study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

The oral bioavailability of niraparib has been determined in rats and dogs ([Section 5.1.2](#)), but has yet to be determined in human subjects, including those with cancer. Therefore, this study will examine the absolute oral bioavailability of niraparib and the absorption, metabolism, excretion, and mass balance of oral [<sup>14</sup>C]-niraparib in subjects with cancer.

The oral dose of niraparib used in this study is 300 mg, which is the MTD of niraparib ([Section 5.1.3.1.1](#)). A total of 144 subjects have been treated with niraparib up to 400 mg QD in Phase 1 studies, and the 300-mg daily dose of niraparib is considered safe and generally well tolerated (IB version 3.0, 09 April [2014](#)). The 300-mg daily dose of niraparib is currently being administered in 2 Phase 3 studies ([Section 5.1.3.2](#)).

This study will be the first-in-human administration of the IV formulation of niraparib. Data from the nonclinical studies did not demonstrate any safety issues that would preclude testing of IV niraparib in humans, and a microdose (100 µg) of niraparib is being administered in the current study.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Primary Objective**

- To determine the absolute bioavailability of niraparib by using an IV niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer.

### **6.2. Secondary Objectives**

- To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer.
- To evaluate the safety and tolerability of niraparib in subjects with cancer.

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is an open-label study with 2 parts, including an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with GCP.

**Part 1:** The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of  $100 \mu\text{g}$  niraparib, containing approximately  $1 \mu\text{Ci}$  of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and PK blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** The Screening Visit will occur within the 3 weeks prior to study drug administration. All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately  $100 \mu\text{Ci}$  of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3 \mu\text{Ci}$  of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. When subjects are not confined to the study center, urine and fecal samples will be collected via a courier service every 24 hours. For either the urine or fecal sample, if the total radioactivity in the Day 15 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 29. As long as the radioactivity remains

higher than 0.1% of the dose given, samples will continue to be collected every 24 hours on a weekly schedule.

**Extension study:** On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). Subjects have 7 days to complete the screening assessments. The Screening Visit should occur between 1 and 7 days after the last dose of study drug (Part 1 or Part 2). The Cycle 1/Day 1 Visit can occur on the same day as the Screening Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [ $3 \times 100\text{-mg}$  capsules, unlabeled active pharmaceutical ingredient] of niraparib) and will undergo safety assessments and PK blood sampling. (QD)No fasting period is required during the extension study. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg ( $2 \times 100\text{-mg}$  capsules) QD and subsequently to 100 mg ( $1 \times 100\text{-mg}$  capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.

**Roll-over study (all eligible subjects):** Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

The schedule of assessments for Part 1, Part 2, and the extension study are presented in [Table 1](#), [Table 2](#), and [Table 3](#), respectively.

## 7.2. Number of Subjects

There will be 6 subjects in Part 1 of the study and 6 subjects in Part 2 of the study. Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects will be eligible to participate in the open-label extension study.

## 7.3. Treatment Assignment

At the Screening Visit, subjects will be offered the option to participate in either part of the study until 1 part of the study is fully enrolled, at which time subjects can only be screened for the remaining part of the study, or for future replacements ([Section 8.4.1](#)).

## 7.4. Dose Adjustment Criteria

During the extension study, dose interruption or reduction will be allowed based on treatment side effects. Treatment must be interrupted for any nonhematologic National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.02; [HHS 2009](#)) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days, the subject may restart treatment with niraparib, but with a dose level reduction according to Table 5 if prophylaxis is not considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted. Dose reductions for any CTCAE Grade 2 events that are bothersome to the subject will be permitted per the Investigator's judgment.

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 28-day dose interruption period, and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

**Table 5: Niraparib Dose Reductions for Nonhematologic Toxicities**

Event <sup>a</sup>	Dose <sup>b</sup>
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE $\geq$ 28 days	Discontinue study drug

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; QD, once a day; SAE, serious adverse event.

<sup>a</sup> Dose reductions for any NCI-CTCAE Grade 2 events that are bothersome to the subject will be permitted per the Investigator's judgment.

<sup>b</sup> Dose not to be decreased below 100 mg QD.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts, as outlined in [Table 6](#).

**Table 6: Niraparib Dose Modification/Reduction for Hematologic Toxicities**

Event	Dose Modification
Platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at the same dose or a reduced dose based on clinical judgment.
Second occurrence of platelet count 75,000-99,999/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count $< 75,000/\mu\text{L}$	Study drugs must be interrupted until platelet counts are $\geq 100,000/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophils $< 1000/\mu\text{L}$	Study drugs must be interrupted until neutrophil counts are $\geq 1500/\mu\text{L}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin $< 8 \text{ g/dL}$	Study drugs must be interrupted until hemoglobin is $\geq 9 \text{ g/dL}$ with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviation: CBC, complete blood count.

If dose interruption or modification is required at any point on study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for CBC will be required for an additional 28 days after the AE has been resolved to the specified levels, after which monitoring every 28 days may resume. Weekly blood draws for CBC can be collected either at the study center or local laboratories. If the hematologic toxicity has not recovered to the specified levels within 28 days of the dose interruption period and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

For major surgery while on treatment, up to 28 days of drug interruption is allowed.

Once the dose of study drug has been reduced, any re-escalation must be discussed with the Medical Monitor.

All dose interruptions and reductions (including any missed doses) and the reasons for the interruptions and reductions will be recorded in the electronic case report form (eCRF).

## 7.5. Criteria for Study Termination

If in the opinion of the Investigator or Sponsor there is reasonable or sufficient cause, this study may be prematurely terminated at any time. Written notification documenting the reason for study termination will be provided to the Investigator or Sponsor by the terminating party. Circumstances that may warrant termination include study center performance issues, a potential new finding with the study drug, or changes in the development program. See [Section 8.4](#) for subject withdrawal criteria. Additional circumstances include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enroll subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of study drug

Should the study be stopped prematurely, all study materials must be returned to the Sponsor or be disposed of according to the Sponsor's specifications.

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## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a PARP inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL} (5.6 \text{ mM})$
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. AST and ALT  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
8. Subject is able to take oral medications.

### 8.2. Subject Exclusion Criteria

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS)

disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.

4. Subject has known hypersensitivity to the components of niraparib.
5. Subject has had major surgery within 3 weeks of study drug administration or has not recovered from all effects of any major surgery.
6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
7. Subject received a transfusion (platelets or red blood cells) within 4 weeks of study drug administration.
8. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
9. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
10. Subject is immunocompromised with an active event and is being treated with medications.
11. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
12. Subject has a baseline QTc prolongation of >470 msec at the Screening Visit.
13. Subject is receiving concomitant medication(s) that prolong QTc ([Appendix 20.1](#)).
14. Subject is starting chemotherapy within 3 weeks of study drug administration.
15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
16. Subject has a history of illicit drug use.
17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
18. Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of study drug administration.

19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months or within 30 days prior to study drug administration for subjects participating in Parts 1 and 2, respectively.

### **8.3. Restrictions During Study**

Restrictions during the study include the following:

1. If sexually active, subjects of reproductive potential and their partners must agree to the use of 2 of the following highly effective forms of contraception throughout their participation in the study and for 90 days after the last dose of study drug:
  - Condom with spermicide and one of the following:
    - Oral contraceptive or hormonal therapy (eg, hormone implants)
    - Placement of an intrauterine device

Acceptable nonhormonal birth control methods include the following:

- Total sexual abstinence
- Vasectomized sexual partner and use of a male condom, with subject assurance that partner received postvasectomy confirmation of azoospermia
- Tubal occlusion and use of a male condom with spermicide
- Intrauterine device and use of a male condom with spermicide

Acceptable hormonal methods with use of a male condom with spermicide include the following:

- Etonogestrel implants (eg, Implanon®, Norplant®)
- Normal and low dose combined oral pills
- Norelgestromin/ethynodiol dihydrogesterone transdermal system.
- Intravaginal device (eg, ethynodiol dihydrogesterone and etonogestrel)
- Cerazette® (desogestrel), which is currently the only highly efficacious progesterone-based pill

2. No other anticancer therapy is permitted during the course of study treatment for any subject. If the subject discontinues study drug, this restriction no longer applies. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.
3. Prophylactic cytokine (granulocyte colony-stimulating factor) administration should not be given in the first cycle of the extension study but may be administered in subsequent cycles according to local guidelines.
4. An increased risk of infection with the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are

unknown, so live virus and bacterial vaccines should not be administered to subjects in the study.

5. Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to receiving study drug and/or within 6 hours after receiving study drug.
6. Subjects who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.
7. Subjects should try to minimize their exposure to ultraviolet light, including natural or artificial sunlight (tanning beds or ultraviolet A or B treatment), while taking niraparib to avoid any possibility of phototoxicity. If subjects need to be outdoors while taking niraparib, they should wear loose fitting clothes and hats that protect skin from direct sun exposure and discuss other sun protection measures with their physician, such as ultraviolet-protection sunscreen. If a sunburn-like reaction or skin eruption occurs, subjects should contact their physician.

#### **8.4. Subject Withdrawal Criteria**

A subject may be discontinued from treatment or from the study for the following reasons:

- AE
  - For the extension study only, a treatment-related CTCAE Grade 3 or 4 AE that has not reverted to CTCAE Grade 1 or less within 28 days. At the Investigator's discretion, following dose interruption (no longer than 28 days), subjects may be considered for dose reductions ([Section 7.4](#)), providing they have not already undergone the maximum number of 2 dose reductions allowed. If a CTCAE Grade 3 or 4 AE recurs upon rechallenging with study drug at the lowest allowable dose, the subject must permanently discontinue treatment.
- Unacceptable toxicity
  - For the extension study only, if the subject experiences a dose interruption or modification because of a hematologic toxicity and the platelet count has not reverted to  $\geq 100,000/\mu\text{L}$  within 28 days, the subject should be discontinued.
- Severe noncompliance with the protocol, as judged by the Investigator and/or Sponsor.
- Subject becomes pregnant
- It is in the best interest of the subject, as judged by the Investigator and/or Sponsor
- Subject withdraws consent
- Sponsor decision to terminate study
- For the extension study only, disease progression and/or clinical criteria per standard of care

Subjects who discontinue from treatment will continue to receive follow-up safety assessments (see [Section 12](#)) as part of the study for 30 days from the last dose, unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the subject, who is at any time and for any reason free to discontinue their participation in the study, without prejudice to further treatment
- Death
- Loss to follow-up

If a subject is lost to follow-up or withdraws from study treatment, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.

#### **8.4.1. Replacement of Subjects**

After consultation between the Sponsor and the Principal Investigator (PI), enrollment may be extended to replace subject(s) discontinued during the study. Replacement subjects will be assigned the next available dosing number for the part of study in which the discontinued subjects were enrolled.

## 9. TREATMENT OF SUBJECTS

### 9.1. Description of Study Drug

The investigational products that will be used in this study are summarized in Table 7.

**Table 7: Investigational Product**

	Investigational Product		
<b>Product Name</b>	niraparib	[ <sup>14</sup> C]-niraparib IV solution	[ <sup>14</sup> C]-niraparib
<b>Dosage Form</b>	100-mg capsules	sterile solution for IV administration	capsules
<b>Unit Dose</b>	300 mg (3 × 100-mg capsules)	100 µg (1 µCi total radioactivity)	300 mg (3 × 100-mg capsules, 3 x 33.3 µCi of radioactivity [100 µCi total radioactivity])
<b>Route of Administration</b>	oral	IV	oral
<b>Study Phase Taken</b>	Part 1 and Extension	Part 1	Part 2

Abbreviation: IV, intravenous.

### 9.2. Prior and Concomitant Medications

Any medication the subject takes during the study other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication.

All prior and concomitant medications will be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Known prior medications that exclude a subject from participating in the study are described in the Exclusion Criteria ([Section 8.2](#)). Prohibited concomitant medications are described in [Section 8.3](#). Additionally, niraparib has potential to induce CYP1A2. Therefore, subjects should be advised to use caution when taking medications that are also inducers of CYP1A2. Examples of CYP1A2 inducers include montelukast, phenytoin, moricizine, omeprazole, and phenobarbital ([HHS 2012](#)). Niraparib is a substrate for P-gp; therefore, subjects should be advised to use caution when taking medications that are inhibitors or inducers of P-gp. Examples of P-gp inhibitors include the following ([HHS 2012](#)): amiodarone, azithromycin, captorpril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and

verapamil. Examples of P-gp inducers include the following (HHS 2012): avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir-ritonavir.

### **9.3. Treatment Compliance**

The study staff will maintain an ongoing record of the dispensing and administration of study drug for each subject. For the extension study, subjects will be instructed to return any unused study drug to the study center during their visit on the first day of each cycle or at EOT. Drug accountability will be performed on capsules dispensed versus returned to the study center at each visit and the number of days since the last visit.

### **9.4. Randomization and Blinding**

Subjects will not be randomly assigned and instead may choose in which part of the study to participate ([Section 7.3](#)). This is an unblinded study.

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Study Drug**

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor.

### **10.2. Study Drug Packaging and Labeling**

Niraparib 100-mg capsules (unlabeled active pharmaceutical ingredient) will be packed in high-density polyethylene bottles with child-resistant closures. Each dosing container will contain a sufficient number of capsules for 1 treatment cycle. Niraparib will be dispensed to subjects on Day 1 of every cycle of the extension study.

The IV solution and oral capsules will be prepared for dosing by Quotient Clinical from [<sup>14</sup>C]-niraparib active pharmaceutical ingredient following Good Manufacturing Practices. Information on the preparation, packaging, and labeling of the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity per 300-mg dose) of niraparib can be found in the investigational medicinal product dossier.

### **10.3. Study Drug Storage**

The 100-mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 15°C to 25°C. Until study drug is dispensed to the subjects, the study drug will be stored in a suitable container, at storage conditions specified by the Sponsor, in a securely locked area, accessible to authorized personnel only.

Information for storing the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity) of niraparib can be found in the investigational medicinal product dossier.

### **10.4. Study Drug Administration**

For Part 1, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For Part 2, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity ( $3 \times 100\text{-mg}$  capsules, labeled active pharmaceutical ingredient [ $3 \times 33.3\text{ }\mu\text{Ci}$  of radioactivity]), on Day 1 after an overnight fast of at least 10 hours. Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration. Subjects will continue fasting until

4 hours after administration of study drug, at which time a light meal will be served. The total fasting time for Day 1 is approximately 14 hours.

For the extension study, 300 mg of niraparib ( $3 \times 100\text{-mg}$  capsules, unlabeled active pharmaceutical ingredient) will be administered orally QD until the subject meets 1 of the withdrawal criteria (Section 8.4); dose interruptions and reductions will be allowed based on treatment side effects (Section 7.4). No fasting period is required during the extension study. Subjects will be instructed to take the niraparib dose at the same time of day, preferably in the morning. The first dose will be administered at the study center. Subjects must swallow and not chew the capsules, and the consumption of water is permissible.

## **10.5. Study Drug Accountability**

The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes the subject number, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as “returned” and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. When the study monitor visits the site, he or she will reconcile the drug accountability log with the products stored in the pharmacy.

## **10.6. Study Drug Handling and Disposal**

After receiving Sponsor approval in writing, the study center is responsible for returning all unused or partially used study drug to Sponsor or a designated third party or for preparing the study drug for destruction at the investigational study center.

## 11. PHARMACOKINETIC ASSESSMENTS

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 2](#).

### 11.1. Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling

For Part 1, blood samples for PK analysis will be collected at the following times: predose (0 hour within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 (immediately after infusion), 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 2 [ $\pm 2$  min], 3 [ $\pm 2$  min], 6 [ $\pm 5$  min], and 12 [ $\pm 15$  min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For the extension study, blood samples will be collected for PK analysis at the following times: Cycle 1/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours  $\pm 15$  min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).

The exact time that each sample is collected will be recorded by the study center, regardless of whether the sample is collected within the specified windows. A detailed description of the blood sample schedule and aliquot collection is included in [Table 8](#) and [Table 9](#) for Parts 1 and 2, respectively. Blood samples that will be used to measure the plasma concentration of [ $^{14}\text{C}$ ]-niraparib with accelerator mass spectrometry (AMS) in Part 1 will be transferred for analysis. Refer to the laboratory manual for further details on sample handling and shipping.

**Table 8: Part 1 Blood Sample Schedule and Aliquot Collection**

Day From Oral Dose	Time From Oral Dose	Time From Start of IV Infusion (hour)	Blood Samples for AMS Plasma Analysis of IV Dose (mL) <sup>a</sup>	Blood Samples for LC-MS/MS Plasma Analysis of Oral Dose (mL) <sup>b</sup>	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	—	2	2	2
	1 hr [±2 min]	—	—	2	2
	1.5 hr [±2 min]	—	—	2	2
	2 hr [prior to IV infusion]	0 (predose)	2	2	8
	2.125 hr [±1 min]	0.125	2	—	4
	2.25 hr [immediately after infusion]	0.25	2	—	4
	2.33 hr [±1 min]	0.33	2	—	4
	2.66 hr [±1 min]	0.66	2	—	4
	3 hr [±2 min]	1	2	2	8
	4 hr [±5 min]	2	2	2	8
	6 hr [±5 min]	4	2	2	8
	12 hr [± 15 min]	10 [±1]	2	2	8
2	24 hr [±1 hr]	22 [±1]	2	2	2
3	48 hr [±2 hr]	46 [±2]	2	2	2
4	72 hr [±4 hr]	70 [±4]	2	2	2
5	96 hr [±4 hr]	94 [±4]	2	2	2
7	144 hr [±4 hr]	142 [±4]	2	2	2
9	192 hr [±8 hr]	190 [±8]	2	2	2
11	240 hr [±12 hr]	238 [±12]	2	2	2
13	288 hr [±12 hr]	286 [±12]	2	2	2
15	336 hr [±12 hr]	334 [±12]	2	2	2
22	504 hr [±12 hr]	502 [±12]	2	2	2

Abbreviations: AMS, accelerator mass spectrometry; IV, intravenous; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

<sup>a</sup> These samples will include 1 sample for immediate AMS analysis (2 mL), and 1 sample that will be used as either a back-up sample for AMS analysis or potentially for LC-MS/MS analysis (2 mL).

<sup>b</sup> These samples will include 1 sample for immediate analysis (2 mL) and 1 back-up sample (2 mL).

**Table 9: Part 2 Blood Sample Schedule and Aliquot Collection**

Day	Time From Oral Dose	Blood Samples for LC-MS/MS Plasma Analysis <sup>a</sup> (mL)	Blood Sample for LSC Plasma Analysis (mL)	Blood Sample for LSC Whole Blood Analysis (mL)	Metabolite Profiling LC-MS/LC-MS/MS (mL)	Total Blood Sample Volume (mL)
1	0 (predose, within 30 min prior to dose)	2	2	2	2	10
	1 hr [ $\pm 2$ min]	2	2	2	2	10
	1.5 hr [ $\pm 2$ min]	2	2	2	—	8
	2 hr [ $\pm 2$ min]	2	2	2	2	10
	3 hr [ $\pm 2$ min]	2	2	2	2	10
	4 hr [ $\pm 5$ min]	2	2	2	—	8
	6 hr [ $\pm 5$ min]	2	2	2	2	10
	12 hr [ $\pm 15$ min]	2	2	2	2	10
2	24 hr [ $\pm 1$ hr]	2	2	2	2	10
3	48 hr [ $\pm 2$ hr]	2	2	2	2	10
4	72 hr [ $\pm 4$ hr]	2	2	2	2	10
5	96 hr [ $\pm 4$ hr]	2	2	2	2	10
6	120 hr [ $\pm 4$ hr]	2	2	2	2	10
8	168 hr [ $\pm 4$ hr]	2	2	2	2	10
11	240 hr [ $\pm 12$ hr]	2	2	2	2	10
15	336 hr [ $\pm 12$ hr]	2	2	2	2	10
22	504 hr [ $\pm 12$ hr]	2	2	2	2	10

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> These samples will include 1 sample for immediate analysis (2 mL), and 1 back-up sample (2 mL).

## 11.2. Urine Sample Collection

Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and

then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the urine sample schedule and the aliquot collection is included in Table 10. Refer to the laboratory manual for further details on sample storage conditions.

**Table 10: Urine Sample Schedule and Aliquot Collection**

Day	Interval (hour)	Niraparib Concentration LC-MS/MS Analysis (mL)	Radioactivity LSC Analysis (mL)	Metabolite Profiling LC-MS /LC-MS/MS (mL)	Total Urine Sample Volume (mL)
1	0 (predose)		2 × 3	3 × 10	37
	0-12				
	12-24				
2	24-36		1		
	36-48				
3	48-72				
4	72-96				
5	96-120				
6	120-144				
7	144-168				
8	168-192				
9	192-216				
10	216-240				
11	240-264				
12	264-288				
13	288-312				
14	312-336				
15 <sup>a</sup>	336-360				

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

### 11.3. Fecal Sample Collection

Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the fecal sample schedule and the aliquot collection is included in Table 11. Refer to the laboratory manual for further details on sample storage conditions.

**Table 11: Fecal Sample Schedule and Aliquot Collection**

Day	Time (hour)	Aliquot Collection
1	0 (predose)	Fecal samples will be processed per stool and analyzed in 24-hour intervals.
	0-24	
2	24-48	
3	48-72	
4	72-96	
5	96-120	
6	120-144	
7	144-168	
8	168-192	
9	192-216	
10	216-240	
11	240-264	
12	264-288	
13	288-312	
14	312-336	
15 <sup>a</sup>	336-360	

Abbreviation: LC-MS/MS, liquid chromatography-tandem mass spectrometry ;LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

## 11.4. Sample Analysis

Analysis of blood, urine, and fecal samples includes the following:

- **Blood:** Blood samples will be analyzed for the plasma concentration of niraparib using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Part 1 blood samples will be analyzed for the plasma concentration of [<sup>14</sup>C]-niraparib using AMS. Part 2 blood samples will be analyzed for the whole blood and plasma concentrations of [<sup>14</sup>C]-niraparib using liquid scintillation counting (LSC). Part 2 plasma blood samples will be analyzed for metabolite profiling and identification using high resolution liquid chromatography-mass spectrometry (LC-MS), in combination with LC-MS/MS (including ion trap instruments). A quantitative LC-MS/MS method will be established for niraparib and the major carboxylic acid metabolite.
- **Urine:** Radioactivity content in urine samples will be determined by LSC. The concentration of niraparib will be determined with LC-MS/MS. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).
- **Fecal:** Radioactivity content in fecal samples will be determined by LSC. Metabolite profiling and identification will be carried out using high resolution LC-MS, in combination with LC-MS/MS (including ion trap instruments).

Pharmacokinetic parameters of interest include the following:

- **Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ; time to reach  $C_{max}$  ( $T_{max}$ ); and AUC from time 0 to the last quantifiable concentration ( $AUC_{0-last}$ ); and if the data allow: AUC from time 0 to infinity ( $AUC_{0-inf}$ ); apparent oral volume of distribution ( $Vd/F$ ); apparent oral clearance ( $CL/F$ ); and  $t_{1/2}$ . Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.
- **Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ ,  $Vd/F$ ,  $CL/F$ , and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$  (day), and total amount of drug excreted in the urine,  $A_e$  (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption ( $f$ ), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.

- **Extension study:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ , and  $t_{1/2}$ .

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## 12. ASSESSMENT OF SAFETY

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 7.1](#).

### 12.1. Safety Parameters

#### 12.1.1. Demographic and Baseline Characteristics

The following demographic information will be documented during the Screening Visit for Parts 1 and 2:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (Asian, Black, Caucasian, Other, Unknown)

The following baseline characteristics will be documented during the Screening Visit for Parts 1 and 2:

- History of drug, alcohol, or other substance abuse
- History of psychiatric illness
- Smoking history

#### 12.1.2. Medical History and Cancer History

Major medical history will be collected during the Screening Visit for Parts 1 and 2. Medical history will be obtained by interviewing the subjects or by reviewing their medical records.

Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis. CT scans should be performed per standard of care. If the subject discontinues due to disease progression, then the CT scan closest to the time of progression (EOT) should also be provided.

The following will be documented for cancer history:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Date of start of first treatment
- Agents used in first treatment
- Date of last dose of first treatment
- Dates of start of all subsequent treatments

- Agents used in all subsequent treatments
- Dates of last dose of all subsequent treatments
- Date of recurrence for each treatment

#### **12.1.3. Prior and Concomitant Medications**

For prior medications, subjects will be asked during the Screening Visit for Parts 1 and 2 what medications they have taken during the last 30 days. All concomitant medications will be recorded from the time the subject signs the informed consent form (ICF) through completion of the study.

#### **12.1.4. Vital Signs**

Blood pressure, pulse rate, and aural (tympanic) temperature will be measured while the subject is in the supine position at every visit that the subject is at the study center (see [Table 1](#), [Table 2](#), and [Table 3](#) for time points) after the subject has been resting for approximately 2 minutes. Vital signs will be collected prior to study drug administration on Day 1.

#### **12.1.5. Weight, Height, and Body Mass Index**

Height (cm) and weight (kg) will be measured without shoes during the Screening Visit for Parts 1 and 2, and body mass index ( $\text{kg}/\text{m}^2$ ) will be calculated. For Parts 1 and 2, weight will also be measured at the Day -1 Visit and the Day 22 Visit. For the extension study, weight will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

#### **12.1.6. Physical Examination**

The physical examination includes an assessment of general appearance and a review of body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems).

For Parts 1 and 2, the physical examination will be performed at the Screening Visit and at the Day 22 Visit. For the extension study, the physical examination will be performed at the Cycle 1/Day 1 Visit, Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at EOT.

#### **12.1.7. Electrocardiogram**

The 12-lead ECG will be performed during the Screening Visit for Parts 1 and 2, the Day 1 Visit (predose and 2 hours postdose) for Parts 1 and 2, the Day 22 Visit for Parts 1 and 2, the Day 1 Visit (predose and 2 hours postdose) for each cycle during the extension study, and at EOT. Subjects will be in the supine position and resting for approximately 2 minutes before ECGs are recorded. For the measurement of QTc prolongation at the Screening Visit, results will include a mean of triplicate ECG readings (3 readings in rapid succession not more than 2 minutes apart).

### **12.1.8. Laboratory Assessments**

Laboratory assessments will be performed by the local laboratory at the study center. Blood samples should be drawn prior to study drug administration.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the study center. The Investigator or designee will indicate whether or not the value is of clinical significance and whether or not the subject requires intervention or further monitoring. Clinical significance will be defined as that requiring medical intervention. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality is found in the samples taken during the study, it should be recorded as an AE, and the subject will be followed until the test has normalized or stabilized.

#### **12.1.8.1. Parts 1 and 2 Laboratory Assessments**

Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio.

Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

Assessments will be conducted at the Screening Visit, the Day -1 Visit, and Day 22 Visit for Part 1; and the Day -1, 15, and 22 Visits for Part 2.

For the hematology assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

#### **12.1.8.2. Extension Study Laboratory Assessments**

The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. The CBC will be conducted at the Screening Visit, Day 1 (only if the Screening Visit and Cycle 1/Day 1 Visit occur on the same day [ie, CBC does not need to be conducted at the Screening Visit and again at Day 1 Visit]) Days 8, 15, and 22 of Cycle 1; Day 1 of every new cycle; and EOT.

Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. These assessments will be measured at the Screening Visit, Day 1 (only if the Screening Visit and Cycle 1/Day 1 Visit occur on the same day [ie, coagulation assessments do not need to be conducted at the Screening Visit and again at Day 1 Visit]), the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and EOT.

If the laboratory assessments for the Screening Visit are performed on the same day as the Cycle 1/Day 1 Visit, the results will be reviewed prior to dosing.

For the CBC, 3 mL of blood will be collected. For the coagulation assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **12.1.9. Laboratory Screenings**

#### **12.1.9.1. Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Screening**

Testing for HBV, HCV, and HIV will only be performed during the Screening Visit for Parts 1 and 2 if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

#### **12.1.9.2. Pregnancy Screen**

A serum pregnancy test will be performed for women of childbearing potential according to standard local procedures during the Screening Visit for Parts 1 and 2. All subjects who do not continue to the extension study will have a serum pregnancy test prior to study exit. Subjects who continue to the extension study will have a serum pregnancy test at the screening visit and at treatment discontinuation for the extension study. A urine pregnancy test will be performed during the Screening Visit for the extension study and every 3 months thereafter (Cycle 4, Cycle 7, etc.).

### **12.1.10. Eastern Cooperative Oncology Group Performance Scale**

The ECOG performance scale assesses the subject's general well-being and activities of daily life ([Appendix 20.2](#)). To be eligible for enrollment into this study, subjects must have an ECOG performance status of 0 to 2 during the Screening Visit for Parts 1 and 2. ECOG assessments will be conducted at the Parts 1 and 2/Day 22 Visit for subjects who are not enrolling in the extension study. The ECOG performance status will be reassessed during the extension study at the Screening Visit, the Day 1 Visit for Cycle 2 and each subsequent cycle, and at EOT. The same observer should assess performance status each time.

## **12.2. Adverse and Serious Adverse Events**

### **12.2.1. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be documented.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study treatment has been administered.

#### **12.2.1.2. Serious Adverse Event**

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:

- Results in death
  - This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)
  - An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

A distinction should be drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

### **12.2.1.3. Submission of Expedited Reports to Regulatory Authority, Sites, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

Per regulatory requirements, if an SAE report is required to be submitted to a Regulatory Authority a copy of this report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigators/site. TESARO or its designee will submit a copy of the report to their respective IRB or IEC.

## **12.3. Relationship to Study Drug**

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.
- Likely related: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.
- Unlikely to be related: A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.
- Unrelated: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

## **12.4. Recording Adverse Events**

AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see [Table 1](#), [Table 2](#), and [Table 3](#) for schedules of events). All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center.

Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the above SAE reporting process.

Abnormal laboratory values that constitute an AE or SAE must be collected. Investigators should assess the severity of AEs according to CTCAE ([HHS 2009](#)).

In general, CTCAE version 4.02 severity grades are the following:

- Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under [Section 12.2.1.2](#). An AE of severe intensity may not be considered serious.

## 12.5. Reports of Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report notification form and reported to the Sponsor.

Pregnancies occurring in subjects enrolled in a study or in a female partner of a male subject must be reported and followed to outcome. The Investigator is responsible for documenting the course and outcome of any pregnancy that occurs while a subject is enrolled in the study and any pregnancy that occurs within 90 days after a subject's last dose.

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death,

congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see [Section 12.6](#)).

The investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The Investigator should follow-up with the subject or the subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs after the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor, or designee, within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs.

#### PREGNANCY CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

#### 12.6. Reporting Adverse Events

The Investigator must report any SAE once he/she becomes aware of within 24 hours of becoming aware of the event. SAEs must be reported using the following contact information:

#### SAE REPORTING CONTACT INFORMATION

Email: PI [REDACTED]

Fax: PI [REDACTED]

Telephone: PI [REDACTED]

For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report Form must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant

and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the subject's personal identifiers (eg, subject name, medical record number) removed according to local regulations. The Investigator must sign and date all SAE forms.

*The minimum information required for an initial SAE report is:*

- Name of person sending the report (ie, name, address of Investigator)
- Subject identification (screening/randomization number, initials, NOT subject name)
- Protocol number
- Description of SAE
- Causality assessment

In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information

## **13. STATISTICS**

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined in this section. Any deviations from the planned analyses will be described in the final integrated clinical study report.

### **13.1. General Considerations**

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum value, and maximum value). Categorical data will be summarized using counts and percentages. All data will be listed in data listings.

### **13.2. Study Population**

#### **13.2.1. Subject Disposition**

The number and percentage of subjects who enter and complete the study will be presented by group (ie, Part 1 subjects, Part 2 subjects, and extension study subjects). Subjects who fail to complete the study will be summarized and categorized by reason for termination (lost to follow-up, AE, etc.). In addition, the numbers of subjects in each analysis set will be summarized by group

#### **13.2.2. Demographic Information and Baseline Characteristics**

Demographics and baseline characteristics will be summarized descriptively by group and will be summarized for each of the defined analysis sets.

#### **13.2.3. Prior and Concomitant Medications**

Medications will be coded according to the current version of the World Health Organization Drug Dictionary. Prior and concomitant medications will be summarized descriptively by group.

#### **13.2.4. Protocol Deviations**

Protocol deviations will be listed by subject and a summary of significant protocol deviations by type will be produced.

#### **13.2.5. Analysis Populations**

**Safety Population:** All subjects who received study drug

**Pharmacokinetic Population:** All subjects who received study drug and provide adequate PK samples to calculate PK parameters

## **13.3. Safety Analyses**

### **13.3.1. Adverse Events**

AE terms will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing an event will be summarized

for each system organ class and preferred term by group. Likewise, AEs will also be tabulated according to intensity and relationship to study drug. Serious AEs, discontinuation due to AEs, and deaths will also be presented and listed separately, including the relationship to study drug.

### **13.3.2. Physical Examinations**

Physical examination findings will be summarized descriptively by group and by study visit. Individual data listings of physical examination findings will be presented for each subject.

### **13.3.3. Vital Signs**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for vital signs. Individual data listings of vital signs will be presented for each subject. Flags will be attached to values outside of the reference limits along with the PI's assessment of clinical significance. Clinically significant vital signs will be summarized separately by group and study visit, and individual data listings of clinically significant vital signs will also be presented for each subject.

### **13.3.4. Electrocardiograms**

Observed values at baseline and changes from baseline will be summarized descriptively by group and study visit for the ECG parameters, including PR interval and QTc. Individual data listings of ECGs will be presented for each subject. Flags will be attached to QTc values of clinical significance. Clinically significant ECG parameters will be summarized separately by group, and individual data listings of clinically significant ECG parameters will also be presented for each subject.

### **13.3.5. Clinical Laboratory Assessments**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for the clinical laboratory results. Individual data listings of clinical laboratory results will be presented for each subject. Shift tables will also be presented for select chemistry and hematology laboratory parameters. Flags will be attached to values outside of the laboratory's reference limits along with the PI's assessment of clinical significance. Clinically significant laboratory values will be summarized separately by group and study visit, and individual data listings of clinically significant laboratory results will also be presented for each subject.

## **13.4. Pharmacokinetic Analyses**

### **13.4.1. Part 1**

Plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

#### **13.4.2. Part 2**

Whole blood and plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

#### **13.4.3. Extension Study**

Plasma concentrations of niraparib based on mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics.

### **13.5. Determination of Sample Size**

The sample size of 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) is not based on statistical considerations and instead represents a balance between the number of subjects exposed and accounts for interindividual variability. Enrollment may be extended to replace subjects discontinued during the study ([Section 8.4.1](#)).

### **13.6. Data Monitoring**

An external Data Safety Monitoring Board will not be established for this study. The Sponsor will monitor safety throughout the project through the following efforts:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of nonserious AEs as they are recorded in the eCRF or appear in the source documents at the study center
- Periodic teleconferences with the PI to share experiences and ensure communication

Findings discovered to have immediate implication for the management of subjects on study treatment will be communicated to the PI in the timeframe associated with unexpected and drug-related SAEs.

Safety surveillance will include routine monitoring of clinical laboratory results, physical examination findings, vital signs, AE reporting, and ECG monitoring.

## 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

### 14.1. Study Monitoring

Before the study center can enter a subject into the study, a representative of the Sponsor or a designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or a representative will have regular contacts with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented in eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met the criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### 14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC, or an IRB may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

### **14.3. Ethics Committee**

The PI must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study, including the subject ICF and recruitment materials, must be maintained by the PI and made available for inspection.

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## **15. QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its representative may conduct a quality assurance audit. Refer to [Section 14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The PI must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### **16.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsor's policy on Bioethics.

### **16.3. Written Informed Consent**

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

The Sponsor or its representative will be allowed to conduct study center visits at the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **17.2. Retention of Records**

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **18. PUBLICATION POLICY**

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

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## 19. LIST OF REFERENCES

- Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245-51.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361(2):123-34.
- Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-61.
- Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res*. 2012;18(6):1726-34.
- Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-92.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
- TESARO, Inc. Niraparib. Investigator's brochure, Version 3.0. Waltham (MA); 2014. 115 p.
- Thompson JL and Crossman RR. Drug-induced QT prolongation. *US Pharm*. 2007;32(2):44-50.
- United States Department of Health and Human Services (HHS). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. 2009 [cited 30 Jan 2014]. Available from: [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE\\_4.02\\_2009-09-15\\_QuickReference\\_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf).
- United States Department of Health and Human Services (HHS), Food and Drug Administration, Center for Drug Evaluation and Research. Draft guidance. Drug interaction studies – Study design, data analysis, implications for dosing, and labeling recommendations. February 2012 [cited 04 Feb 2014]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>.

## 20. APPENDICES

### 20.1. Drugs Associated with QT Prolongation

Table 12: Drugs Associated with QT prolongation

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Itraconazole	Venlafaxine		Metoclopramide
	Azithromycin			Domperidone
				Ondansetron
				Diphenhydramine

Sources:

Thompson and Crossman, 2007

CredibleMeds web site. <https://www.crediblemeds.org>

US Pharmacist web site. Drug-induced QT prolongation page. Available at:

[http://www.uspharmacist.com/content/d/featured\\_articles/c/10396/](http://www.uspharmacist.com/content/d/featured_articles/c/10396/). Accessed 12 November 2013.

Cardiac Risk in the Young sponsored web site on Sudden Arrhythmic Death Syndrome. Available at:

[http://www.sads.org.uk/drugs\\_to\\_avoid.htm](http://www.sads.org.uk/drugs_to_avoid.htm). Accessed 24 October 2014.

## 20.2. Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Reference: [Oken et al, 1982](#)

**1. TITLE PAGE**

**NIRAPARIB**  
**PR-30-5015-C**

**ABSORPTION, METABOLISM, EXCRETION, AND THE  
DETERMINATION OF ABSOLUTE BIOAVAILABILITY  
OF NIRAPARIB IN SUBJECTS WITH CANCER**

**EudraCT No:** 2014-002011-41

**Sponsor:** TESARO, Inc

1000 Winter Street, Suite 3300  
Waltham, MA 02451 USA

PI [REDACTED]

PI [REDACTED] MD, MPH

Senior Medical Director

PI [REDACTED]

PI [REDACTED], MD, PhD

PI [REDACTED]

PI [REDACTED], NL

PI [REDACTED]

**Contract Research Organization:**

PPD  
929 North Front Street  
Wilmington, NC 28401 USA

**Version of Protocol:**

1.0

**Final Protocol Date:**

28 May 2014

TESARO, Inc  
Protocol: PR-30-5015-C (version 1.0)

Niraparib  
Version Date: 28 May 2014

### INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for niraparib. I have read the PR-30-5015-C protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

PI	Name of Inv
_____ Signature of Investigator	
26-05-2014 Date	

## SIGNATURE PAGE

### Declaration of Sponsor or Responsible Medical Expert

**Protocol Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer (Protocol Number PR-30-5015-C)

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2008) and the guidelines on Good Clinical Practice (GCP) applicable to this clinical study.

#### Sponsor Signatory

PI [REDACTED] \_\_\_\_\_  
MD, PhD \_\_\_\_\_  
Chief Medical Officer \_\_\_\_\_  
TESARO, Inc \_\_\_\_\_  
Date 11 May 2014

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> TESARO, Inc	
<b>Name of Investigational Product:</b> Niraparib	
<b>Name of Active Ingredient:</b> (3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl} piperidine (tosylate monohydrate salt)	
<b>Title of Study:</b> Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer (Protocol Number PR-30-5015-C)	
<b>Study center(s):</b> A single study center in the Netherlands.	
<b>Principal Investigator:</b> Dr PI [REDACTED], MD, PhD <b>Investigators:</b> Not applicable	
<b>Studied period (years):</b> Estimated date first subject enrolled: December 2014 Estimated date last subject completed: December 2015	<b>Phase of development:</b> 1
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"><li>To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer.</li></ul> <b>Secondary:</b> <ul style="list-style-type: none"><li>To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer.</li><li>To evaluate the safety and tolerability of niraparib in subjects with cancer.</li></ul>	
<b>Methodology:</b> This is an open-label study with 2 parts, including an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP). <b>Part 1:</b> After the Screening Visit (occurring within the 3 weeks prior to study drug administration), subjects will be admitted to the study center the afternoon prior to study drug administration (ie, Study Day -1, at least 12 hours prior to study drug administration). After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day -1 to the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous	

physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** After the Screening Visit (occurring within the 3 weeks prior to study drug administration), subjects will be admitted to the study center the afternoon prior to study drug administration (ie, Study Day -1, at least 12 hours prior to study drug administration). After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu$ Ci of radioactivity, on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day -1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. When subjects are not confined to the study center, urine and fecal samples will be collected via a courier service every 24 hours. For either the urine or fecal sample, if the total radioactivity in the Day 15 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, samples will continue to be collected every 24 hours on a weekly schedule.

**Extension study:** On the same day that subjects complete Part 1 or 2 of the study, subjects will be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). Subjects have 7 days to complete the screening assessments, and the Screening Visit (+7 days) and Cycle 1/Day 1 Visit can occur on the same day. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3  $\times$  100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib once a day [QD]) and will undergo safety assessments and PK blood sampling. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 21 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm$ 3] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2  $\times$  100-mg capsules) QD and subsequently to 100 mg (1  $\times$  100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)). At treatment discontinuation, safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at treatment discontinuation.

**Number of subjects (planned):**

**Part 1:** 6 subjects

**Part 2:** 6 subjects

Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects will be eligible to participate in the open-label extension study.

**Diagnosis and main criteria for inclusion:**

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL}$  (5.6 mM)
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Male and female subjects of childbearing potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
7. Subject is able to take oral medications.

**Exclusion criteria:**

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of the Screening Visit, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
4. Subject has known hypersensitivity to the components of niraparib.
5. Subject has had major surgery within 3 weeks of the Screening Visit or has not recovered from all effects of any major surgery.
6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord

<p>compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.</p> <p>7. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.</p> <p>8. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.</p> <p>9. Subject is immunocompromised with an active event and is being treated with medications.</p> <p>10. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).</p> <p>11. Subjects has a baseline corrected QT interval (QTc) prolongation of &gt;470 msec at the Screening Visit.</p> <p>12. Subject is receiving concomitant medication(s) that prolong QTc (<a href="#">Appendix 20.1</a>).</p> <p>13. Subject has been treated with a known PARP inhibitor.</p> <p>14. Subject is starting chemotherapy within 3 weeks of the Screening Visit.</p> <p>15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours of study drug administration.</p> <p>16. Subject has a history of illicit drug use.</p> <p>17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to the Screening Visit) or dependence or is unable to abstain from alcohol for the duration of the study.</p> <p>18. Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of the Screening Visit.</p> <p>19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months or within 30 days prior to study drug administration for subjects participating in Parts 1 and 2, respectively.</p>
<p><b>Investigational product, dosage and mode of administration:</b></p> <p><b>Part 1:</b> Niraparib 300 mg (3 × 100-mg capsules) orally and [<sup>14</sup>C]-niraparib 100 µg (1 µCi total radioactivity) intravenously</p> <p><b>Part 2:</b> [<sup>14</sup>C]-niraparib 300 mg (capsules; 100 µCi total radioactivity) orally</p> <p><b>Extension study:</b> Niraparib 300 mg (3 × 100-mg capsules) orally</p>
<p><b>Duration of treatment:</b></p> <p><b>Part 1:</b> Administration of a single oral dose, followed by a 15-minute IV infusion 2 hours after administration of the single oral dose</p> <p><b>Part 2:</b> Administration of a single oral dose</p> <p><b>Extension study:</b> once daily administration until treatment discontinuation</p>
<p><b>Reference therapy, dosage and mode of administration:</b></p> <p>None.</p>
<p><b>Criteria for evaluation:</b></p>

**Pharmacokinetics:**

**Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters: maximum observed plasma concentration ( $C_{max}$ ); time to reach  $C_{max}$  ( $T_{max}$ ); and area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration ( $AUC_{0-last}$ ); and if the data allow: AUC from time 0 to infinity ( $AUC_{0-inf}$ ); apparent oral volume of distribution (Vd/F); apparent oral clearance (CL/F); and half-life ( $t_{1/2}$ ). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

**Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$ , and if the data allow:  $AUC_{0-inf}$ , Vd/F, CL/F, and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e$ (day), and total amount of drug excreted in the urine,  $A_e$ (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption (f), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.

**Extension study:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ , and  $t_{1/2}$ .

**Safety:**

Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.

**Statistical methods:**

**Pharmacokinetics:**

Whole blood (Part 2 only) and plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

**Safety:**

All AEs will be listed and tabulated. Physical examination findings, vital signs, ECG parameters, and clinical laboratory results will be listed and summarized using descriptive statistics.

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#### 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 1: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event
A <sub>e</sub> (day)	Amount of drug excreted in the urine in a 24-hour period
A <sub>e</sub> (total)	Total amount of drug excreted in the urine
ALT	Alanine aminotransferase
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC <sub>0-inf</sub>	Area under the plasma concentration-time curve from time 0 to infinity
AUC <sub>0-last</sub>	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
CA-125	Cancer antigen 125
CBC	Complete blood count
CL/F	Apparent oral clearance
C <sub>max</sub>	Maximum observed plasma concentration
CNS	Central nervous system
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
f	Extent of absorption
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Homologous recombination

Abbreviation or Specialist Term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LSC	Liquid scintillation counting
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
P-gp	P-glycoprotein
PARP	Poly (adenosine diphosphate-ribose) polymerase
PI	Principal Investigator The Investigator who leads the study conduct at an individual study center. Every study center has a Principal Investigator.
PK	Pharmacokinetic
QD	Once a day
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
t <sub>½</sub>	Half-life
T <sub>max</sub>	Time to reach maximum observed plasma concentration
ULN	Upper limit of normal
Vd/F	Apparent oral volume of distribution

## 5. INTRODUCTION

### 5.1. Niraparib

Niraparib ([3S]-3-[4-(7-(aminocarbonyl)-2H-indazol-2-yl) phenyl] piperidine [tosylate monohydrate salt]) is an orally active poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor with nanomolar potency that is being developed for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway or that are driven by PARP-mediated transcription factors.

#### 5.1.1. DNA Repair, Cancer, and PARP Inhibition

The PARP-1 and -2 enzymes, which are zinc-finger DNA-binding enzymes, play a crucial role in DNA repair. Upon formation of single-strand DNA breaks, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones, various DNA repair proteins, and PARP itself, which results in chromatin relaxation and fast recruitment of DNA repair factors that access and repair DNA breaks.

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of tumor cells than on normal cells. Therefore, a hypothesis is that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways.

Clinical studies have shown that PARP inhibitors have antitumor activity in certain types of cancer (Fong et al, 2009; Audeh et al, 2010; Gelmon et al, 2011; Kummar et al, 2012; Ledermann et al, 2012). Nonclinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with homozygous inactivation of either *BRCA-1* or *BRCA-2*; these breast cancer genes are known to be important in the HR DNA repair pathway. Germline mutations of *BRCA-1* and -2 are found in the majority of subjects with inherited breast or ovarian cancer. Inactivation of *BRCA-1* and -2 by mechanisms other than mutations, including somatic mutations and gene silencing by promoter hypermethylation, occurs in a significant portion of several sporadic cancers. In particular, for ovarian cancer, somatic *BRCA-1* or -2 mutations are found in 10% to 15% of all epithelial ovarian carcinomas, and strongly reduced expression of *BRCA-1* has been observed in a significant portion of sporadic ovarian cancers. Collectively, up to 40% to 60% of ovarian cancers might be responsive to PARP inhibitors as a consequence of defects in the BRCA-HR pathway, indicating a great potential for this approach in the therapy of ovarian cancer.

#### 5.1.2. Niraparib Nonclinical Studies

Niraparib inhibits normal DNA repair mechanisms and induces synthetic lethality when administered to cells with HR defects. In a *BRCA-1* mutant xenograft study in mice, niraparib dosed orally caused tumor regression, which was mirrored by a greater than 90% reduction in

tumor volume compared to control. In a *BRCA-2* mutant xenograft study in mice, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib was evaluated for its potential effects on cardiovascular and neurological function using several experimental safety pharmacology models. Niraparib inhibited the hERG current with an  $IC_{50}$  value of 10  $\mu$ M and an  $IC_{20}$  value of 3.8  $\mu$ M. Niraparib was administered intravenously during 3 sequential 30-minute periods at 1, 3, and 10 mg/kg to determine the effect of niraparib on cardiovascular function in 3 anesthetized dogs. Niraparib had no effect on the corrected QT interval (QTc; average plasma concentration  $\leq$ 15.3  $\mu$ M at 10 mg/kg). Mean arterial pressure and heart rate were increased at all doses evaluated, but the QRS cardiac interval was only increased at 10 mg/kg. Niraparib had no effect on neurological function in conscious mice at a single oral dose of 100 mg/kg.

The pharmacokinetics of niraparib in male Sprague-Dawley rats were determined following intravenous (IV; 3 mg/kg) and oral (5 mg/kg) administration. In male beagle dogs, pharmacokinetic (PK) studies were conducted following IV (1 mg/kg) and oral (3 mg/kg) administration. Following IV administration, niraparib demonstrated moderate-to-high clearance (28 and 31 mL/min/kg), a high volume of distribution (6.9 and 12.3 L/kg), and moderate terminal half-lives (3 and 6 hours) in rats and dogs, respectively. The oral bioavailability of niraparib was reasonable in both species (approximately 27% in rats and 57% in dogs).

Niraparib was investigated in 1-month oral toxicity studies in order to support daily dosing of the compound in humans, where niraparib was administered to rats and dogs by oral gavage once a day (QD) for up to 4 weeks followed by an approximately 2-week recovery period. Overall, nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. In the 1-month repeat-dose toxicity study in rats, mortality and physical signs were limited to the high dose (50 mg/kg/day). All changes observed at 50 mg/kg/day were resolved at the end of the 2-week recovery period or demonstrated reversibility, except for minimal treatment-related arterial hypertrophy in the heart and increased trabecula in the bone. At 10 mg/kg/day, there were no treatment-related changes other than increased urine volume in males. Based on these findings, the no observed adverse effect level (NOAEL) in the rat study was 10 mg/kg/day. The dose causing severe irreversible toxicity and death was 50 mg/kg/day. In the dog, decreases in hematology values were observed at a dose of 15 mg/kg/day, and all hematology changes seen during the dosing phase were resolved at the end of the recovery period. Although a decrease in amount of spermatogenic epithelium was observed after 1-month dosing at 6 mg/kg/day and 15 mg/kg/day and was not resolved at the end of the 2-week recovery period, the continued presence of spermatogenic epithelium supports that this change would eventually resolve. Therefore, based on these findings, the NOAEL for the dog study was 3 mg/kg/day.

The niraparib nonclinical studies are described in detail in the Investigator's Brochure ([TESARO 2014](#)).

### **5.1.3. Niraparib Clinical Studies**

The niraparib clinical studies are described in detail in the Investigator's Brochure ([TESARO 2014](#)).

### 5.1.3.1. Phase 1 Studies

Niraparib has been evaluated in a series of Phase 1 clinical studies in subjects with solid tumors. For these studies, niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide. As of 15 November 2013, 144 subjects have been treated with oral niraparib at doses up to 400 mg QD in Phase 1 studies, and treatment with niraparib has been generally well tolerated.

The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were (n=144): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), rash (10.4%), dizziness (9.7%), electrocardiogram (ECG) QT prolonged (9.7%), pyrexia (9.7%), abdominal distension (9.0%), urinary tract infection (9.0%), weight decreased (9.0%), abdominal pain lower (8.3%), alopecia (8.3%), neoplasm malignant (8.3%), dry mouth (7.6%), hypoalbuminemia (7.6%), musculoskeletal pain (7.6%), stomatitis (7.6%), arthralgia (6.9%), blood creatinine increase (6.9%), chills (6.9%), dyspepsia (6.9%), hypomagnesemia (6.9%), paresthesia (6.9%), aspartate aminotransferase (AST) increased (6.3%), dehydration (6.3%), musculoskeletal chest pain (6.3%), neck pain (6.3%), alanine aminotransferase (ALT) increased (5.6%), dysgeusia (5.6%), myalgia (5.6%), and palpitations (5.6%).

The most commonly reported drug-related (>5.0%) AEs (all grades) in the clinic were (n=129): fatigue (45.1%), nausea (42.4%), anemia (41.0%), thrombocytopenia (32.6%), decreased appetite (23.6%), neutropenia (22.2%), vomiting (22.2%), constipation (19.4%), leukopenia (18.1%), diarrhea (10.4%), insomnia (8.3%), dyspnea (6.9%), ECG QT prolonged (6.9%), headache (6.3%), stomatitis (6.3%), hyponatremia (5.6 %), and alopecia (5.6%).

#### 5.1.3.1.1. Study PN001

The maximum tolerated dose (MTD) of niraparib dosed orally QD was determined to be 300 mg in subjects with advanced solid tumors or hematologic malignancies. The dose-limiting toxicity for niraparib is thrombocytopenia, with Grade 4 thrombocytopenia reported in 2 of 6 subjects treated at the 400-mg dose level. For the 44 subjects treated at the MTD, 21 subjects experienced thrombocytopenia, 16 subjects experienced neutropenia, and 34 subjects experienced anemia.

During routine safety monitoring, 12 of 104 subjects reported AEs of prolonged QTc (6 subjects experienced a Grade 1 event, 5 subjects experienced a Grade 2 event, and 1 subject experienced a Grade 3 event). Preliminary evaluation showed 8 of these subjects (7.7%) had QT prolongation that was assessed as at least possibly related to study drug. Of these 8 subjects, 7 received 300 mg of niraparib QD and 1 received 210 mg of niraparib QD. A total of 8 subjects exceeded a 30-msec change from baseline during the study, with the maximum being 70 msec. Given that these were spontaneous reports, and not part of a controlled QTc evaluation, it would be difficult to assess the relationship to niraparib. Until a more rigorous evaluation of QTc can be conducted, subjects should be evaluated for QTc prolongation.

A preliminary analysis of plasma drug concentration profiles indicated that the maximum observed plasma concentration ( $C_{max}$ ) after oral dosing occurred at approximately 3 hours. There was an approximate 3- to 4-fold accumulation in the area under the plasma concentration-time curve (AUC),  $C_{max}$ , and plasma concentration at 24 hours postdose from Cycle 1/Day 1 to Cycle 2/Day 1. Mean apparent terminal half-life ( $t_{1/2}$ ) ranged from 32.8 to 46.0 hours over the 60- to 400-mg dose range. Pharmacokinetic parameters appeared to be dose-proportional.

Although efficacy was not the primary objective for this Phase 1 study, antitumor activity was observed in subjects taking niraparib as monotherapy at oral dose levels ranging from 60 to 400 mg. Based on Investigator evaluation using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or cancer antigen 125 (CA-125) criteria, an overall response rate of 13% was observed for all subjects in this study. Analysis of the 20 *BRCA* mutant ovarian cancer subjects enrolled in the study demonstrated that this group showed a 35% overall response rate according to RECIST version 1.1 and/or CA-125 criteria.

#### **5.1.3.2. Phase 3 Studies**

The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, HER2 negative, germline *BRCA* mutation breast cancer subjects (PR-30-5010-C) and to platinum-sensitive ovarian cancer subjects (PR-30-5011-C). A total of 55 subjects had been randomized in the Phase 3 clinical study program as of 07 January 2014. Preliminary results from 15 subjects who completed the PR-30-5011-C study suggest administration of niraparib with food is expected to have a negligible effect on the pharmacokinetics of niraparib. Of the 16 subjects enrolled in the PR-30-5011-C study as of 15 November 2013, the most commonly reported AEs were gastrointestinal disorders (constipation, nausea, and vomiting) and metabolism and nutrition disorders (decreased appetite).

#### **5.1.4. Risks and Benefits**

The potential benefit of niraparib treatment for patients with cancer is tumor regression.

Nonclinical toxicology testing of niraparib did not produce any untoward effects to prevent clinical investigation. The most commonly reported AEs in the clinic for the Phase 1 studies, where niraparib was used in combination with chemotherapies, including carboplatin, carboplatin/paclitaxel, carboplatin/liposomal doxorubicin, pegylated liposomal doxorubicin, and temozolomide, were (Section 5.1.3.1): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), and rash (10.4%). The Investigator should monitor subjects closely for these AEs.

As Phase 1 studies have shown that niraparib is safe and well tolerated, the potential benefits outweigh the potential risks.

When taking niraparib, caution should be used when also taking medications that are inducers of CYP1A2 or inhibitors or inducers of P-glycoprotein (P-gp; Section 9.2).

## 5.2. Rationale for Current Study

This is an open-label study with 2 parts, including an extension study following completion of Parts 1 or 2, that is being conducted in approximately 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) with cancer to examine the absorption, metabolism, excretion, and absolute bioavailability of niraparib. This study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

The oral bioavailability of niraparib has been determined in rats and dogs ([Section 5.1.2](#)), but has yet to be determined in human subjects, including those with cancer. Therefore, this study will examine the absolute oral bioavailability of niraparib and the absorption, metabolism, excretion, and mass balance of oral [<sup>14</sup>C]-niraparib in subjects with cancer.

The oral dose of niraparib used in this study is 300 mg, which is the MTD of niraparib ([Section 5.1.3.1.1](#)). A total of 144 subjects have been treated with niraparib up to 400 mg QD in Phase 1 studies, and the 300-mg daily dose of niraparib is considered safe and generally well tolerated ([TESARO 2014](#)). The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies ([Section 5.1.3.2](#)).

This study will be the first-in-human administration of the IV formulation of niraparib. Data from the nonclinical studies did not demonstrate any safety issues that would preclude testing of IV niraparib in humans, and a microdose (100 µg) of niraparib is being administered in the current study.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Primary Objective**

- To determine the absolute bioavailability of niraparib by using an IV niraparib microdose of 100 µg (containing approximately 1 µCi of [<sup>14</sup>C]-niraparib) in subjects with cancer.

### **6.2. Secondary Objectives**

- To characterize the absorption, metabolism, and excretion of [<sup>14</sup>C]-niraparib administered as a single, 300-mg oral dose (containing approximately 100 µCi of [<sup>14</sup>C]-niraparib) to subjects with cancer.
- To evaluate the safety and tolerability of niraparib in subjects with cancer.

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is an open-label study with 2 parts, including an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with GCP.

**Part 1:** After the Screening Visit (occurring within the 3 weeks prior to study drug administration), subjects will be admitted to the study center the afternoon prior to study drug administration (ie, Study Day -1, at least 12 hours prior to study drug administration). After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg ( $3 \times 100\text{-mg}$  capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of  $100 \mu\text{g}$  niraparib, containing approximately  $1 \mu\text{Ci}$  of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day -1 to the morning of Day 4, and subjects will undergo safety assessments and PK blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.

**Part 2:** After the Screening Visit (occurring within the 3 weeks prior to study drug administration), subjects will be admitted to the study center the afternoon prior to study drug administration (ie, Study Day -1, at least 12 hours prior to study drug administration). After an overnight fast of at least 10 hours, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately  $100 \mu\text{Ci}$  of radioactivity, on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day -1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. When subjects are not confined to the study center, urine and fecal samples will be collected via a courier service every 24 hours. For either the urine or fecal sample, if the total radioactivity in the Day 15 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 sample is detected to be higher than 0.1% of the radioactivity of the dose given, samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, samples will continue to be collected every 24 hours on a weekly schedule.

**Extension study:** On the same day that subjects complete Part 1 or 2 of the study, subjects will be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified

in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). Subjects have 7 days to complete the screening assessments, and the Screening Visit (+7 days) and Cycle 1/Day 1 Visit can occur on the same day. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib QD) and will undergo safety assessments and PK blood sampling. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 21 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [ $\pm 3$ ] days) to receive study drug and for safety assessments, PK blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ([Section 8.4](#)). At treatment discontinuation, safety assessments, PK blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at treatment discontinuation.

The schedule of assessments for Part 1, Part 2, and the extension study are presented in [Table 2](#), [Table 3](#), and [Table 4](#), respectively.

**Table 2: Schedule of Assessments: Part 1**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X	X											X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>c</sup>	X												
Clinical laboratory assessments <sup>d</sup>	X	X				X							X
Serum pregnancy test	X												
Electrocardiogram (12-lead) <sup>e</sup>	X		X										X
ECOG performance status	X												
Confirm diagnosis with CT scan <sup>f</sup>	X												
Screening number assignment	X												
Subject confinement		X	X	X	X	X							
Subject dosing number assignment			X										
Niraparib oral administration <sup>g</sup>			X										

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
[ <sup>14</sup> C]-niraparib IV infusion <sup>b</sup>			X										
Pharmacokinetic blood sampling <sup>c</sup>			X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous.

<sup>a</sup> Subjects will be admitted to the study center the afternoon prior to study drug administration (at least 12 hours prior to study drug administration).

<sup>b</sup> Vital signs include blood pressure, pulse rate, and oral temperature. Vital signs will be collected prior to study drug administration on Day 1 and prior to any blood draws on other study days.

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>d</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. On Day 1, blood samples should be drawn prior to study drug administration.

<sup>e</sup> Subjects will have a 12-lead electrocardiogram at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>f</sup> Subjects must provide a CT scan to confirm their diagnosis. A CT scan is performed every 8 weeks as part of standard of care.

<sup>g</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>h</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>i</sup> Blood samples for pharmacokinetic analysis will be collected at the following times: predose (0 hour), Day 1 (1, 1.5, 2 [prior to IV infusion], 2.125, 2.25, 2.33, 2.66, 3, 4, 6, and 12 [ $\pm$ 1] hours postdose), Day 2 (24 [ $\pm$ 1] hours postdose), Day 3 (48 [ $\pm$ 2] hours postdose), Day 4 (72 [ $\pm$ 4] hours postdose), Day 5 (96 [ $\pm$ 4] hours postdose), Day 7 (144 [ $\pm$ 4] hours postdose), Day 9 (192 [ $\pm$ 8] hours postdose), Day 11 (240 [ $\pm$ 12] hours postdose), Day 13 (288 [ $\pm$ 12] hours postdose), Day 15 (336 [ $\pm$ 12] hours postdose), and Day 22 (504 [ $\pm$ 12] hours postdose).

**Table 3: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																	
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup> End of Part 2
Informed consent	X																	
Subject demographics and baseline characteristics	X																	
Medical history and cancer history	X																	
Inclusion/exclusion criteria	X																	
Physical examination	X																X	
Height (cm)	X																	
Weight (kg)	X	X															X	
Body mass index (kg/m <sup>2</sup> )	X																	
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X				X	X	
HBV/HCV/HIV screening <sup>d</sup>	X																	
Clinical laboratory assessments <sup>e</sup>	X	X															X	X
Serum pregnancy test	X																	
Electrocardiogram (12-lead) <sup>f</sup>	X		X														X	
ECOG performance status	X																	
Confirm diagnosis with CT scan <sup>g</sup>	X																	
Screening number assignment	X																	
Subject confinement		X	X	X	X	X	X	X	X	X	X	X						

Assessment or Procedure	Day Relative to First Dose of Study Drug																	
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup> End of Part 2
Subject dosing number assignment		X																
[ <sup>14</sup> C]-niraparib administration <sup>b</sup>		X																
Pharmacokinetic blood sampling <sup>c</sup>			X	X	X	X	X	X		X			X				X	X
Blood sample for metabolite profiling <sup>d</sup>			X	X	X	X	X	X		X			X				X	X
Urine collection <sup>e</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal collection <sup>f</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> Subjects will be admitted to the study center the afternoon prior to study drug administration (at least 12 hours prior to study drug administration).

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote k and Footnote l), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and oral temperature. Vital signs will be collected prior to study drug administration on Day 1 and prior to any blood draws on other study days.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. On Day 1, blood samples should be drawn prior to study drug administration.

<sup>f</sup> Subjects will have a 12-lead electrocardiogram at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>g</sup> Subjects must provide a CT scan to confirm their diagnosis. A CT scan is performed every 8 weeks as part of standard of care.

<sup>h</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity, after an overnight fast of at least 10 hours.

Subjects will continue fasting until 4 hours after administration of study drug.

- <sup>i</sup> Blood samples for pharmacokinetic analysis will be collected at the following times: predose (0 hour), Day 1 (1, 1.5, 2, 3, 4, 6, and 12 [ $\pm 1$ ] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).
- <sup>j</sup> Blood samples for metabolite profiling will be collected at the following times: predose (0 hour), Day 1 (1, 2, 3, 6, and 12 [ $\pm 1$ ] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).
- <sup>k</sup> Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.
- <sup>l</sup> Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

**Table 4: Schedule of Assessments: Open-label Extension Study**

Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b,c</sup>	Treatment Discontinuation <sup>d</sup>
		Day 1	Day 8	Day 15	Day 21		
Inclusion/exclusion criteria <sup>e</sup>	X	X					
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>f</sup>	X	X	X	X	X	X	X
Complete blood count <sup>g</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>h</sup>	X			X		X	X
Pregnancy test <sup>i</sup>	X					X	X
Study drug dispensed/collected <sup>j</sup>		X				X	X
Electrocardiogram (12-lead) <sup>k</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>l</sup>		X				X	X
Concomitant medication and AE monitoring <sup>m</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> On the same day that subjects complete Part 1 or 2 of the study, subjects will be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in Table 6. Subjects have 7 days to complete the screening assessments, and the Screening Visit (+7 days) and Cycle 1/Day 1 Visit can occur on the same day.

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days.

<sup>c</sup> Visits will continue approximately every 4 weeks until treatment discontinuation.

<sup>d</sup> The visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria.

<sup>e</sup> If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the inclusion/exclusion criteria should only be reviewed once.

<sup>f</sup> Vital signs include blood pressure, pulse rate, and oral temperature. Vital signs will be collected prior to study drug administration and blood draws. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.

<sup>g</sup> The complete blood count includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.

<sup>h</sup> Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.

<sup>i</sup> A urine pregnancy test will be conducted at the Screening Visit and every 3 months thereafter. A serum pregnancy test will be conducted at treatment discontinuation.

<sup>j</sup> Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. No new capsules will be dispensed at treatment discontinuation.

<sup>k</sup> Subjects will have a 12-lead electrocardiogram at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at treatment discontinuation.

<sup>l</sup> Blood samples for pharmacokinetic analysis will be collected at the following times: Cycle 1/Day 1 Visit (predose and 2 hours postdose), Cycle 2/Day 1 Visit (predose and 2 hours postdose), Cycle 4/Day 1 Visit (predose), and Cycle 8/Day 1 Visit (predose).

<sup>m</sup> Serious AEs will be recorded up to 30 days after treatment discontinuation.

## 7.2. Number of Subjects

There will be 6 subjects in Part 1 of the study and 6 subjects in Part 2 of the study. Subjects will only participate in 1 part of the study. Subjects may be replaced until there are 6 evaluable subjects in each part of the study. Following re-review of entry criteria, subjects will be eligible to participate in the open-label extension study.

## 7.3. Treatment Assignment

At the Screening Visit, subjects will be offered the option to participate in either part of the study until 1 part of the study is fully enrolled, at which time subjects can only be screened for the remaining part of the study, or for future replacements ([Section 8.4.1](#)).

## 7.4. Dose Adjustment Criteria

During the extension study, dose interruption or reduction will be allowed based on treatment side effects. Treatment must be interrupted for any nonhematologic National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.02; [HHS 2009](#)) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days, the subject may restart treatment with niraparib, but with a dose level reduction according to [Table 5](#) if prophylaxis is not considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted. Dose reductions for any CTCAE Grade 2 events that are bothersome to the subject will be permitted per the Investigator's judgment.

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 28-day dose interruption period, and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

**Table 5: Niraparib Dose Reductions for Nonhematologic Toxicities**

Event <sup>a</sup>	Dose <sup>b</sup>
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE $\geq$ 28 days	Discontinue study drug

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; QD, once a day; SAE, serious adverse event.

<sup>a</sup> Dose reductions for any NCI-CTCAE Grade 2 events that are bothersome to the subject will be permitted per the Investigator's judgment.

<sup>b</sup> Dose not to be decreased below 100 mg QD.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts, as outlined in Table 6.

**Table 6: Niraparib Dose Modification/Reduction for Hematologic Toxicities**

Event	Dose Modification
Platelet count 75,000-100,000/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq$ 100,000/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at the same dose or a reduced dose based on clinical judgment.
Second occurrence of platelet count 75,000-100,000/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq$ 100,000/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count <75,000/ $\mu$ L	Study drugs must be interrupted until platelet counts are $\geq$ 100,000/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophils <1000/ $\mu$ L	Study drugs must be interrupted until neutrophil counts are $\geq$ 1500/ $\mu$ L with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin <8 g/dL	Study drugs must be interrupted until hemoglobin is $\geq$ 9 g/dL with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviation: CBC, complete blood count.

If dose interruption or modification is required at any point on study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for complete blood count (CBC) will be required for an additional 28 days after the AE has been resolved to the specified levels, after which monitoring every 28 days may resume. Weekly blood draws for CBC can be collected either at the study center or local laboratories. If the hematologic toxicity has not recovered to the specified levels within 28 days of the dose interruption period and/or the subject has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the subject must permanently discontinue treatment with niraparib.

For major surgery while on treatment, up to 28 days of drug interruption is allowed.

Once the dose of study drug has been reduced, any re-escalation must be discussed with the Medical Monitor.

All dose interruptions and reductions (including any missed doses) and the reasons for the interruptions and reductions will be recorded in the electronic case report form (eCRF).

## **7.5. Criteria for Study Termination**

If in the opinion of the Investigator or TESARO there is reasonable or sufficient cause, this study may be prematurely terminated at any time. Written notification documenting the reason for study termination will be provided to the Investigator or TESARO by the terminating party. Circumstances that may warrant termination include study center performance issues, a potential new finding with the study drug, or changes in the development program. Additional circumstances include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enroll subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of study drug

Should the study be stopped prematurely, all study materials must be returned to TESARO or be disposed of according to TESARO's specifications.

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a PARP inhibitor. The diagnosis must be confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelets  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9 \text{ g/dL}$  (5.6 mM)
  - d. Serum creatinine  $\leq 1.5 \times$  the upper limit of normal (ULN) or a calculated creatinine clearance  $\geq 60 \text{ mL/min}$  using the Cockcroft-Gault equation
  - e. Total bilirubin  $\leq 1.5 \times$  ULN or direct bilirubin  $\leq 1 \times$  ULN
  - f. AST and ALT  $\leq 2.5 \times$  ULN unless liver metastases are present, in which case AST and ALT must be  $\leq 5 \times$  ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Male and female subjects of childbearing potential must use adequate birth control for the duration of study participation ([Section 8.3](#)).
7. Subject is able to take oral medications.

### 8.2. Subject Exclusion Criteria

Subjects will not be eligible for study entry if any of the following criteria are met:

1. Subject has undergone palliative radiotherapy within 1 week of the Screening Visit, encompassing  $>20\%$  of the bone marrow.
2. Subject has persistent  $>\text{Grade } 2$  toxicity from prior cancer therapy.
3. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered “controlled,” the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord

compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.

4. Subject has known hypersensitivity to the components of niraparib.
5. Subject has had major surgery within 3 weeks of the Screening Visit or has not recovered from all effects of any major surgery.
6. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
7. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
8. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
9. Subject is immunocompromised with an active event and is being treated with medications.
10. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
11. Subjects has a baseline QTc prolongation of >470 msec at the Screening Visit.
12. Subject is receiving concomitant medication(s) that prolong QTc ([Appendix 20.1](#)).
13. Subject has been treated with a known PARP inhibitor.
14. Subject is starting chemotherapy within 3 weeks of the Screening Visit.
15. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours of study drug administration.
16. Subject has a history of illicit drug use.
17. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to the Screening Visit) or dependence or is unable to abstain from alcohol for the duration of the study.
18. Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of the Screening Visit.
19. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months or within 30 days prior to study drug administration for subjects participating in Parts 1 and 2, respectively.

### 8.3. Restrictions During Study

Restrictions during the study include the following:

1. Subjects of childbearing potential and their partners who are sexually active must agree to the use of 2 of the following highly effective forms of contraception throughout their participation in the study and for 90 days after the last dose of study drug:
  - Condom with spermicide and one of the following:
    - Oral contraceptive or hormonal therapy (eg, hormone implants).
    - Placement of an intrauterine device.

Acceptable nonhormonal birth control methods include the following:

- Total sexual abstinence.
- Vasectomized sexual partner and use of a male condom, with subject assurance that partner received postvasectomy confirmation of azoospermia.
- Tubal occlusion and use of a male condom with spermicide.
- Intrauterine device and use of a male condom with spermicide.

Acceptable hormonal methods with use of a male condom with spermicide include the following:

- Etonogestrel implants (eg, Implanon®, Norplant®).
- Normal and low dose combined oral pills.
- Norelgestromin/ethynodiol dihydrogesterone transdermal system.
- Intravaginal device (eg, ethynodiol dihydrogesterone and etonogestrel).
- Cerazette® (desogestrel), which is currently the only highly efficacious progesterone-based pill.

2. No other anticancer therapy is permitted during the course of study treatment for any subject. If the subject discontinues study drug, this restriction no longer applies. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.
3. Prophylactic cytokine (granulocyte colony-stimulating factor) administration should not be given in the first cycle of the extension study but may be administered in subsequent cycles according to local guidelines.
4. An increased risk of infection with the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown, so live virus and bacterial vaccines should not be administered to subjects in the study.
5. Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours of receiving study drug.

6. Subjects who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.
7. Subjects should try to minimize their exposure to ultraviolet light, including natural or artificial sunlight (tanning beds or ultraviolet A or B treatment), while taking niraparib to avoid any possibility of phototoxicity. If subjects need to be outdoors while taking niraparib, they should wear loose fitting clothes and hats that protect skin from direct sun exposure and discuss other sun protection measures with their physician, such as ultraviolet-protection sunscreen. If a sunburn-like reaction or skin eruption occurs, subjects should contact their physician.

#### **8.4. Subject Withdrawal Criteria**

A subject may be discontinued from treatment or from the study for the following reasons:

- AE
- Unacceptable toxicity (For the extension study only, if the subject experiences a dose interruption or modification because of a hematologic toxicity and the platelet count has not reverted to >100,000/ $\mu$ L within 28 days, the subject should be discontinued.)
- Severe noncompliance with the protocol, as judged by the Investigator and/or TESARO.
- Subject becomes pregnant.
- It is in the best interest of the subject, as judged by the Investigator and/or TESARO.
- For the extension study only, a treatment-related CTCAE Grade 3 or 4 AE that has not reverted to CTCAE Grade 1 or less within 28 days. At the Investigator's discretion, following dose interruption (no longer than 28 days), subjects may be considered for dose reductions ([Section 7.4](#)), providing they have not already undergone the maximum number of 2 dose reductions allowed. If a CTCAE Grade 3 or 4 AE recurs upon rechallenging with study drug at the lowest allowable dose, the subject must permanently discontinue treatment.
- For the extension study only, until disease progression and/or clinical criteria per standard of care.

Subjects who discontinue from treatment will continue to receive follow-up safety assessments as part of the study unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the subject, who is at any time and for any reason free to discontinue their participation in the study, without prejudice to further treatment.
- Death.
- Loss to follow-up.

##### **8.4.1. Replacement of Subjects**

After consultation between the Sponsor and the Principal Investigator (PI), enrollment may be extended to replace subject(s) discontinued during the study. Replacement subjects will be

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assigned the next available dosing number for the part of study in which the discontinued subjects were enrolled.

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## 9. TREATMENT OF SUBJECTS

### 9.1. Description of Study Drug

The investigational products that will be used in this study are summarized in Table 7.

**Table 7: Investigational Product**

	Investigational Product		
<b>Product Name</b>	niraparib	[ <sup>14</sup> C]-niraparib IV solution	[ <sup>14</sup> C]-niraparib
<b>Dosage Form</b>	100-mg capsules	sterile solution for IV administration	capsules
<b>Unit Dose</b>	300 mg (3 × 100-mg capsules)	100 µg (1 µCi total radioactivity)	300 mg (100 µCi total radioactivity)
<b>Route of Administration</b>	oral	IV	oral
<b>Study Phase Taken</b>	Part 1 and Extension	Part 1	Part 2

Abbreviation: IV, intravenous.

### 9.2. Prior and Concomitant Medications

Prior medications that exclude a subject from participating in the study are described in the Exclusion Criteria ([Section 8.2](#)). Any medication the subject takes during the study other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication. Prohibited concomitant medications are described in [Section 8.3](#).

All prior and concomitant medications will be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

Niraparib has potential to induce CYP1A2. Therefore, use caution when taking medications that are also inducers of CYP1A2. Examples of CYP1A2 inducers include montelukast, phenytoin, moricizine, omeprazole, and phenobarbital ([HHS 2012](#)).

Niraparib is a substrate for P-gp; therefore, use caution when taking medications that are inhibitors or inducers of P-gp.

Examples of P-gp inhibitors include the following ([HHS 2012](#)): amiodarone, azithromycin, ciprofloxacin, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone,

erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil.

Examples of P-gp inducers include the following ([HHS 2012](#)): avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir-ritonavir.

### **9.3. Treatment Compliance**

The study staff will maintain an ongoing record of the dispensing and administration of study drug for each subject. For the extension study, subjects will be instructed to return any unused study drug to the study center during their visit on the first day of each cycle or at treatment discontinuation. Drug accountability will be performed on capsules dispensed versus returned to the study center at each visit and the number of days since the last visit.

### **9.4. Randomization and Blinding**

Subjects will not be randomly assigned and instead may choose in which part of the study to participate ([Section 7.3](#)). This is an unblinded study.

## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Study Drug**

Niraparib ([3S]-3-[4-(7-(aminocarbonyl)-2H-indazol-2-yl) phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor.

### **10.2. Study Drug Packaging and Labeling**

Niraparib 100-mg capsules (unlabeled active pharmaceutical ingredient) will be packed in high-density polyethylene bottles with child-resistant closures. Each dosing container will contain a sufficient number of capsules for 1 treatment cycle. Niraparib will be dispensed to subjects on Day 1 of every cycle of the extension study.

The IV solution and oral capsules will be prepared for dosing by Quotient Clinical from [<sup>14</sup>C]-niraparib active pharmaceutical ingredient following Good Manufacturing Practices. Information on the preparation, packaging, and labeling of the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity) of niraparib can be found in the investigational medicinal product dossier.

### **10.3. Study Drug Storage**

The 100-mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 2°C to 30°C. Until study drug is dispensed to the subjects, the study drug will be stored in a suitable container at storage conditions specified by TESARO in a securely locked area, accessible to authorized personnel only.

Information for storing the IV solution (containing approximately 1 µCi of radioactivity) and oral capsules (containing approximately 100 µCi of radioactivity) of niraparib can be found in the investigational medicinal product dossier.

### **10.4. Study Drug Administration**

For Part 1, subjects will receive a single, 300-mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1 after an overnight fast of at least 10 hours. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served.

For Part 2, subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity, on Day 1 after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served.

For the extension study, 300 mg of niraparib (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) will be administered orally QD until the subject meets 1 of the withdrawal criteria (Section 8.4); dose interruptions and reductions will be allowed based on treatment side effects (Section 7.4). Subjects will be instructed to take the niraparib dose at the same time of day, preferably in the morning. The first dose will be administered at the study

center. Subjects must swallow and not chew the capsules, and the consumption of water is permissible.

#### **10.5. Study Drug Accountability**

The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes the subject number, amount dispensed, and amount returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as “returned” and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for TESARO review. When the study monitor visits, he or she will reconcile the drug accountability log with the products stored in the pharmacy.

#### **10.6. Study Drug Handling and Disposal**

After receiving TESARO approval in writing, the study center is responsible for returning all unused or partially used study drug to TESARO or a designated third party or for preparing the study drug for destruction at the investigational study center.

## 11. PHARMACOKINETIC ASSESSMENTS

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 7.1](#).

### 11.1. Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling

For Part 1, blood samples will be collected for PK analysis at the following times: predose (0 hour), Day 1 (1, 1.5, 2 [prior to IV infusion], 2.125, 2.25, 2.33, 2.66, 3, 4, 6, and 12 [ $\pm 1$ ] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For Part 2, blood samples will be collected for PK analysis at the following times: predose (0 hour), Day 1 (1, 1.5, 2, 3, 4, 6, and 12 [ $\pm 1$ ] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For Part 2, blood samples will be collected for metabolite profiling at the following times: predose (0 hour), Day 1 (1, 2, 3, 6, and 12 [ $\pm 1$ ] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

For the extension study, blood samples will be collected for PK analysis at the following times: Cycle 1/Day 1 Visit (predose and 2 hours postdose), Cycle 2/Day 1 Visit (predose and 2 hours postdose), Cycle 4/Day 1 (predose), and Cycle 8/Day 1 Visit (predose).

The exact time that each sample is collected will be recorded by the study center, regardless of whether the sample is collected within the specified windows. A detailed description of the blood sample schedule and aliquot collection is included in [Table 8](#) and [Table 9](#) for Parts 1 and 2, respectively. Blood samples that will be used to measure the plasma concentration of [ $^{14}\text{C}$ ]-niraparib with accelerator mass spectrometry (AMS) in Part 1 will be transferred for analysis. Refer to the laboratory manual for further details on sample handling and shipping.

**Table 8: Part 1 Blood Sample Schedule and Aliquot Collection**

Day From Oral Dose	Time From Oral Dose (hour)	Time From Start of IV Infusion (hour)	Blood Samples for AMS Plasma Analysis of IV Dose (mL) <sup>a</sup>	Blood Samples for LC-MS/MS Plasma Analysis of Oral Dose (mL) <sup>b</sup>	Total Blood Sample Volume (mL)
1	0 (predose)	—	2	2	2
	1	—	—	2	2
	1.5	—	—	2	2
	2	0 (predose)	2	2	2
	2.125	7.5 minutes	2	—	—
	2.25	15 minutes	2	—	—
	2.3	20 minutes	2	—	—
	2.66	40 minutes	2	—	—
	3	1	2	2	2
	4	2	2	2	2
	6	—4	2	2	2
	12 [±1]	10 [±1]	2	2	2
2	24 [±1]	22 [±1]	2	2	2
3	48 [±2]	46 [±2]	2	2	2
4	72 [±4]	70 [±4]	2	2	2
5	96 [±4]	94 [±4]	2	2	2
7	144 [±4]	142 [±4]	2	2	2
9	192 [±8]	190 [±8]	2	2	2
11	240 [±12]	238 [±12]	2	2	2
13	288 [±12]	286 [±12]	2	2	2
15	336 [±12]	334 [±12]	2	2	2
22	504 [±12]	502 [±12]	2	2	2

Abbreviations: AMS, accelerator mass spectrometry; IV, intravenous; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

<sup>a</sup> These samples will include 1 sample for immediate AMS analysis (2 mL), and 1 sample that will be used as either a back-up sample for AMS analysis or potentially for LC-MS/MS analysis (2 mL).

<sup>b</sup> These samples will include 1 sample for immediate analysis (2 mL) and 1 back-up sample (2 mL).

**Table 9: Part 2 Blood Sample Schedule and Aliquot Collection**

Day	Time From Oral Dose (hour)	Blood Samples for LC-MS/MS Plasma Analysis <sup>a</sup> (mL)	Blood Sample for LSC Plasma Analysis (mL)	Blood Sample for LSC Whole Blood Analysis (mL)	Metabolite Profiling (mL)	Total Blood Sample Volume (mL)
1	0 (predose)	2	2	2	2	10
	1	2	2	2	2	10
	1.5	2	2	2	—	8
	2	2	2	2	2	10
	3	2	2	2	2	10
	4	2	2	2	—	8
	6	2	2	2	2	10
	12 [ $\pm 1$ ]	2	2	2	2	10
2	24 [ $\pm 1$ ]	2	2	2	2	10
3	48 [ $\pm 2$ ]	2	2	2	2	10
4	72 [ $\pm 4$ ]	2	2	2	2	10
5	96 [ $\pm 4$ ]	2	2	2	2	10
6	120 [ $\pm 4$ ]	2	2	2	2	10
8	168 [ $\pm 4$ ]	2	2	2	2	10
11	240 [ $\pm 12$ ]	2	2	2	2	10
15	336 [ $\pm 12$ ]	2	2	2	2	10
22	504 [ $\pm 12$ ]	2	2	2	2	10

Abbreviations: LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> These samples will include 1 sample for immediate analysis (2 mL), and 1 back-up sample (2 mL).

## 11.2. Urine Sample Collection

Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the urine sample schedule and the aliquot collection is included in Table 10. Refer to the laboratory manual for further details on sample storage conditions.

**Table 10: Urine Sample Schedule and Aliquot Collection**

Day	Interval (hour)	LC-MS/MS Analysis (mL)	LSC Analysis (mL)	Metabolite Profiling (mL)	Total Urine Sample Volume (mL)
1	0 (predose)				
	0-12				
	12-24				
2	24-36				
	36-48				
3	48-72				
4	72-96				
5	96-120				
6	120-144				
7	144-168				
8	168-192				
9	192-216				
10	216-240				
11	240-264				
12	264-288				
13	288-312				
14	312-336				
15 <sup>a</sup>	336-360				

Abbreviations: LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.

### 11.3. Fecal Sample Collection

Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours

through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

A detailed description of the fecal sample schedule and the aliquot collection is included in Table 11. Refer to the laboratory manual for further details on sample storage conditions.

**Table 11: Fecal Sample Schedule and Aliquot Collection**

Day	Time (hour)	Aliquot Collection
1	0 (predose)	
	0-24	
2	24-48	
3	48-72	
4	72-96	
5	96-120	Fecal samples will be processed per stool and analyzed in 24-hour intervals.
6	120-144	
7	144-168	
8	168-192	
9	192-216	
10	216-240	
11	240-264	
12	264-288	
13	288-312	
14	312-336	
15 <sup>a</sup>	336-360	

Abbreviation: LSC, liquid scintillation counting.

<sup>a</sup> If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.

## 11.4. Sample Analysis

Analysis of blood, urine, and fecal samples includes the following:

- **Blood:** Blood samples will be analyzed for the plasma concentration of niraparib using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Part 1 blood samples will be analyzed for the plasma concentration of [<sup>14</sup>C]-niraparib using AMS. Part 2 blood samples will be analyzed for the whole blood and plasma concentrations

of [ $^{14}\text{C}$ ]-niraparib using liquid scintillation counting (LSC). Part 2 plasma blood samples will be analyzed for metabolite profiling and identification using high resolution liquid chromatography-mass spectrometry (LC-MS), potentially in combination with LC-MS/MS (including ion trap instruments). A quantitative LC-MS/MS method will be established for niraparib and the major carboxylic acid metabolite.

- **Urine:** Radioactivity content in urine samples will be determined by LSC. The concentration of niraparib will be determined with LC-MS/MS. Metabolite profiling and identification will be carried out using high resolution LC-MS, potentially in combination with LC-MS/MS (including ion trap instruments).
- **Fecal:** Radioactivity content in fecal samples will be determined by LSC. Metabolite profiling and identification will be carried out using high resolution LC-MS, potentially in combination with LC-MS/MS (including ion trap instruments).

Pharmacokinetic parameters of interest include the following:

- **Part 1:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{\max}$ ; time to reach  $C_{\max}$  ( $T_{\max}$ ); and AUC from time 0 to the last quantifiable concentration ( $AUC_{0-\text{last}}$ ); and if the data allow: AUC from time 0 to infinity ( $AUC_{0-\infty}$ ); apparent oral volume of distribution ( $V_d/F$ ); apparent oral clearance ( $CL/F$ ); and  $t_{1/2}$ . Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.
- **Part 2:** Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters:  $C_{\max}$ ,  $T_{\max}$ , and  $AUC_{0-\text{last}}$ . The plasma niraparib concentration will be used to determine the following PK parameters:  $C_{\max}$ ,  $T_{\max}$ , and  $AUC_{0-\text{last}}$ , and if the data allow:  $AUC_{0-\infty}$ ,  $V_d/F$ ,  $CL/F$ , and  $t_{1/2}$ . Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period,  $A_e(\text{day})$ , and total amount of drug excreted in the urine,  $A_e(\text{total})$ . Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption ( $f$ ), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.
- **Extension study:** Plasma niraparib concentrations will be used to determine the following PK parameters:  $C_{\max}$ ,  $T_{\max}$ ,  $AUC_{0-\text{last}}$ ,  $AUC_{0-\infty}$ , and  $t_{1/2}$ .

## 12. ASSESSMENT OF SAFETY

Subjects will undergo the following procedures according to the schedule of assessments presented in [Section 7.1](#).

### 12.1. Safety Parameters

#### 12.1.1. Demographic and Baseline Characteristics

The following demographic information will be documented during the Screening Visit for Parts 1 and 2:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (white, American Indian/Alaska native, Asian, native Hawaiian or other Pacific Islander, black/African American)

The following baseline characteristics will be documented during the Screening Visit for Parts 1 and 2:

- History of drug, alcohol, or other substance abuse
- History of psychiatric illness
- Smoking history

#### 12.1.2. Medical History and Cancer History

Major medical history will be collected during the Screening Visit for Parts 1 and 2. Medical history will be obtained by interviewing the subjects or by inspecting their medical records.

Subjects must provide a previous CT scan to confirm their cancer diagnosis. A CT scan is performed every 8 weeks as part of standard of care.

The following will be documented for cancer history:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Date of start of first treatment
- Agents used in first treatment
- Date of last dose of first treatment
- Dates of start of all subsequent treatments
- Agents used in all subsequent treatments

- Dates of last dose of all subsequent treatments
- Best response for each prior treatment
- Date of recurrence for each treatment

#### **12.1.3. Prior and Concomitant Medications**

Refer to [Section 9.2](#) for a description of prior and concomitant medications. For prior medications, subjects will be asked during the Screening Visit for Parts 1 and 2 what medications they have taken during the last 30 days. All concomitant medications will be recorded from the time the subject signs the informed consent form (ICF) through completion of the study. Medications will be coded according to the World Health Organization Drug Dictionary 01 December 2013.

#### **12.1.4. Vital Signs**

Blood pressure, pulse rate, and oral temperature will be measured while the subject is in the supine position at every visit that the subject is at the study center (see [Table 2](#), [Table 3](#), and [Table 4](#) for time points) after the subject has been resting for approximately 2 minutes. Vital signs will be collected prior to study drug administration and blood draws.

#### **12.1.5. Weight, Height, and Body Mass Index**

Height (cm) and weight (kg) will be measured without shoes during the Screening Visit for Parts 1 and 2, and body mass index ( $\text{kg}/\text{m}^2$ ) will be calculated. For Parts 1 and 2, weight will also be measured at the Day -1 Visit and the Day 22 Visit. For the extension study, weight will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at treatment discontinuation.

#### **12.1.6. Physical Examination**

The physical examination includes an assessment of general appearance and a review of body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems).

For Parts 1 and 2, the physical examination will be performed at the Screening Visit and at the Day 22 Visit. For the extension study, the physical examination will be performed at the Cycle 1/Day 1 Visit, Cycle 1/Day 15 Visit, Day 1 of every new cycle, and at treatment discontinuation.

#### **12.1.7. Electrocardiogram**

The 12-lead ECG will be performed during the Screening Visit for Parts 1 and 2, the Day 1 Visit (predose and 2 hours postdose) for Parts 1 and 2, the Day 22 Visit for Parts 1 and 2, the Day 1 Visit (predose and 2 hours postdose) for each cycle during the extension study, and at treatment discontinuation. Subjects will be in the supine position and resting for approximately 2 minutes before ECGs are recorded. For the measurement of QTc prolongation at the Screening Visit, results will include a mean of triplicate ECG readings (3 readings in rapid succession not more than 2 minutes apart).

### **12.1.8. Laboratory Assessments**

Laboratory assessments will be performed by the local laboratory at the study center. Blood samples should be drawn prior to study drug administration.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the study center. The Investigator or designee will indicate whether or not the value is of clinical significance and whether or not the subject requires intervention or further monitoring. Clinical significance will be defined as that requiring medical intervention. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality is found in the samples taken during the study, it should be recorded as an AE, and the subject will be followed until the test has normalized or stabilized.

#### **12.1.8.1. Parts 1 and 2 Laboratory Assessments**

Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio.

Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

Assessments will be conducted at the Screening Visit; the Day -1, 4, and 22 Visits for Part 1; and the Day -1, 15, and 22 Visits for Part 2.

For the hematology assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

#### **12.1.8.2. Extension Study Laboratory Assessments**

The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. The CBC will be conducted at the Screening Visit; Days 8, 15, and 21 of Cycle 1; Day 1 of every new cycle; and treatment discontinuation.

Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. These assessments will be measured at the Screening Visit, the Cycle 1/Day 15 Visit, Day 1 of every new cycle, and treatment discontinuation.

If the laboratory assessments for the Screening Visit are performed on the same day as the Cycle 1/Day 1 Visit, the results will be reviewed prior to dosing.

For the CBC, 3 mL of blood will be collected. For the coagulation assessment, 3 mL of blood will be collected. For the serum chemistry assessment, 3.5 mL of blood will be collected.

### **12.1.9. Laboratory Screenings**

#### **12.1.9.1. Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Screening**

Testing for HBV, HCV, and HIV will only be performed during the Screening Visit for Parts 1 and 2 if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

#### **12.1.9.2. Pregnancy Screen**

A serum pregnancy test will be performed for women of childbearing potential according to standard local procedures during the Screening Visit for Parts 1 and 2 and at treatment discontinuation for the extension study. A urine pregnancy test will be performed during the Screening Visit for the extension study and every 3 months thereafter.

### **12.1.10. Eastern Cooperative Oncology Group Performance Scale**

The ECOG performance scale assesses the subject's general well-being and activities of daily life ([Appendix 20.2](#)). In order to be eligible for enrollment into this study, subjects need to have an ECOG performance status of 0 to 2 during the Screening Visit for Parts 1 and 2. The ECOG performance status will be reassessed during the extension study at the Screening Visit, the Day 1 Visit for Cycle 2 and each subsequent cycle, and at treatment discontinuation. The same observer should assess performance status each time.

## **12.2. Adverse and Serious Adverse Events**

### **12.2.1. Definition of Adverse Events**

#### **12.2.1.1. Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by TESARO.

Adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (version 16.1).

### 12.2.1.2. Serious Adverse Event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject and may require medical or surgical intervention or treatment to prevent 1 of the outcomes listed above.

Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE.

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by TESARO.

### 12.2.1.3. Suspected Unexpected Serious Adverse Reaction

Any AE that is serious, associated with the use of study drug, and unexpected (defined as not listed in the appropriate section of the current Investigator's Brochure [TESARO 2014]) is referred to as a suspected unexpected serious adverse reaction (SUSAR) and requires the following additional reporting requirements:

- If the SUSAR is fatal or life-threatening, associated with the use of study drug, and unexpected, regulatory authorities, Institutional Review Boards (IRBs), and Independent Ethics Committees (IECs) will be notified within 7 calendar days after the Sponsor or designee learns of the event. Additional follow-up information (cause of death, autopsy report, and hospital report) should be reported within an additional 8 calendar days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of study drug, and unexpected, regulatory authorities, IRBs, and IECs will be notified within 15 calendar days after the Sponsor or designee learns of the event.

The Sponsor or designee will notify the investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of subjects. Follow-up information may be submitted, if necessary.

The Sponsor or designee will also provide annual safety updates to the regulatory authorities, IRBs, and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

### 12.3. Relationship to Study Drug

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.
- Likely related: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.
- Unlikely to be related: A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.
- Unrelated: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

### 12.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center. Clinically significant changes in laboratory values, blood pressure, and pulse rate need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE.

Information about AEs will be collected from signing of the consent form until the end of the study. Serious AE information will be collected from signing of the consent form until 30 days following the last dose of study drug. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Investigators should assess the severity of AEs according to CTCAE ([HHS 2009](#)).

In general, CTCAE version 4.02 severity grades are the following:

- Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.

- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3: Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under [Section 12.2.1.2](#). An AE of severe intensity may not be considered serious.

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report form and reported to the PPD Pharmacovigilance Department staff at the SAE Hotline number at any time.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

## 12.5. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of the consent form until 30 days following the end of treatment exposure. Planned hospitalization will not be considered an SAE (Section 12.2.1.2). Any SAEs considered related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to PPD within 1 business day of the first awareness of the event. The Investigator must complete, sign, and date the SAE pages; verify the accuracy of the information recorded on the SAE pages with the corresponding source documents; and send a copy by fax to the PPD Pharmacovigilance Department staff. The Investigator and staff are encouraged to contact the Medical Monitor and the PPD Pharmacovigilance Department staff at the SAE Hotline number at any time.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the subject's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and faxed within

24 hours of receipt of the information. If a new SAE report form is faxed, then the Investigator must sign and date the form.

The minimum information required for an initial report includes the following:

- Name of person sending the report (ie, name and address of Investigator)
- Patient identification (screening/randomization number, initials, and NOT the subject's name)
- Protocol number
- Description of SAE
- Causality assessment, if possible

However, as many points as possible on the SAE report form should be covered in the initial report, or the completed SAE report form itself must be faxed to the PPD Pharmacovigilance Department staff. In addition, the event must be documented in the eCRF.

After receipt of the initial report, the safety center will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event.

The Investigator and the Sponsor (or the Sponsor's designee) will review each SAE report, and the Sponsor or the Sponsor's designee will evaluate the seriousness and the causal relationship of the event to study drug. In addition, the Sponsor (or the Sponsor's designee) will evaluate the expectedness according to the Investigator's Brochure ([TESARO 2014](#)). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

Additional follow-up information, if required or available, should be faxed within 1 business day of receipt, and this follow-up information should be completed on a follow-up SAE form, placed with the original SAE information, and kept with the appropriate section of the eCRF and/or study file.

TESARO is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB or IEC of all SAEs that occur at his or her study center.

## 13. STATISTICS

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined in this section. Any deviations from the planned analyses will be described in the final integrated clinical study report.

### 13.1. General Considerations

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum value, and maximum value). Categorical data will be summarized using counts and percentages. All data will be listed in data listings.

### 13.2. Study Population

#### 13.2.1. Subject Disposition

The number and percentage of subjects who enter and complete the study will be presented by group (ie, Part A subjects, Part B subjects, and extension study subjects). Subjects who fail to complete the study will be summarized and categorized by reason for termination (lost to follow-up, AE, etc). In addition, the numbers of subjects in each analysis set will be summarized by group

#### 13.2.2. Demographic Information and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by group and will be summarized for each of the defined analysis sets.

#### 13.2.3. Prior and Concomitant Medications

Medications will be coded according to the World Health Organization Drug Dictionary 01 December 2013. Prior and concomitant medications will be summarized descriptively by group.

#### 13.2.4. Protocol Deviations

Protocol deviations will be listed by subject, and a summary of significant protocol deviations by type will be produced.

#### 13.2.5. Analysis Populations

**Safety Population:** All subjects who received study drug.

**Pharmacokinetic Population:** All subjects who received study drug and provide adequate PK samples to calculate PK parameters.

### **13.3. Safety Analyses**

#### **13.3.1. Adverse Events**

Adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (version 16.1). The number and percentage of subjects experiencing an event will be summarized for each system organ class and preferred term by group. Likewise, AEs will also be tabulated according to intensity and relationship to study drug. Serious AEs, discontinuation due to AEs, and deaths will also be presented and listed separately, including the relationship to study drug.

#### **13.3.2. Physical Examinations**

Physical examination findings will be summarized descriptively by group and by study visit. Individual data listings of physical examination findings will be presented for each subject.

#### **13.3.3. Vital Signs**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for vital signs. Individual data listings of vital signs will be presented for each subject. Flags will be attached to values outside of the reference limits along with the PI's assessment of clinical significance. Clinically significant vital signs will be summarized separately by group and study visit, and individual data listings of clinically significant vital signs will also be presented for each subject.

#### **13.3.4. Electrocardiograms**

Observed values at baseline and changes from baseline will be summarized descriptively by group and study visit for the ECG parameters, including PR interval and QTc. Individual data listings of ECGs will be presented for each subject. Flags will be attached to QTc values of clinical significance. Clinically significant ECG parameters will be summarized separately by group, and individual data listings of clinically significant ECG parameters will also be presented for each subject.

#### **13.3.5. Clinical Laboratory Assessments**

Observed values at baseline and changes from baseline will be summarized descriptively by group and by study visit for the clinical laboratory results. Individual data listings of clinical laboratory results will be presented for each subject. Shift tables will also be presented for select chemistry and hematology laboratory parameters. Flags will be attached to values outside of the laboratory's reference limits along with the PI's assessment of clinical significance. Clinically significant laboratory values will be summarized separately by group and study visit, and individual data listings of clinically significant laboratory results will also be presented for each subject.

### **13.4. Pharmacokinetic Analyses**

#### **13.4.1. Part 1**

Plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

#### **13.4.2. Part 2**

Whole blood and plasma concentrations based on the radioactivity and mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics. Metabolic profiles will be summarized in a descriptive manner, and metabolites will be, if appropriate, quantitatively determined and presented.

#### **13.4.3. Extension Study**

Plasma concentrations of niraparib based on mass spectrometry ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics.

### **13.5. Determination of Sample Size**

The sample size of 12 subjects (6 subjects in Part 1; 6 subjects in Part 2) is not based on statistical considerations and instead represents a balance between the number of subjects exposed and accounts for interindividual variability. Enrollment may be extended to replace subjects discontinued during the study ([Section 8.4](#)).

### **13.6. Data Monitoring**

An external Data Safety Monitoring Board will not be established for this study. TESARO will monitor safety throughout the project through the following efforts:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of nonserious AEs as they are recorded in the eCRF or appear in the source documents at the study center
- Periodic teleconferences with the PI to share experiences and ensure communication

Findings discovered to have immediate implication for the management of subjects on study will be communicated to the PI in the timeframe associated with unexpected and drug-related SAEs.

Safety surveillance will include routine monitoring of clinical laboratory results, physical examination findings, vital signs, AE reporting, and ECG monitoring.

## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

Before a study center can enter a subject into the study, a representative of TESARO or a designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of TESARO or its representatives. This will be documented in a Clinical Study Agreement between TESARO and the Investigator.

During the study, a monitor from TESARO or a representative will have regular contacts with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to TESARO.
- Confirm AEs and SAEs have been properly documented in eCRFs and confirm any SAEs have been forwarded to TESARO, and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### **14.2. Audits and Inspections**

Authorized representatives of TESARO, a regulatory authority, an IEC, or an IRB may visit the study center to perform audits or inspections, including source data verification. The purpose of a TESARO audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact TESARO immediately if contacted by a regulatory agency about an inspection.

#### **14.3. Ethics Committee**

The PI must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study, including the subject consent form and recruitment materials, must be maintained by the PI and made available for inspection.

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## **15. QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with GCP and all applicable regulatory requirements, TESARO or its representative may conduct a quality assurance audit. Refer to [Section 14.2](#) for more details regarding the audit process.

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## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The PI must submit written approval to TESARO before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. TESARO will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### **16.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and TESARO's policy on Bioethics.

### **16.3. Written Informed Consent**

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

TESARO or its representative will be allowed to conduct study center visits at the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **17.2. Retention of Records**

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for TESARO or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

## **18. PUBLICATION POLICY**

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

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## 19. LIST OF REFERENCES

- Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):245-51.
- Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361(2):123-34.
- Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-61.
- Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res*. 2012;18(6):1726-34.
- Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-92.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
- TESARO, Inc. Niraparib. Investigator's brochure, Version 3.0. Waltham (MA); 2014. 115 p.
- Thompson JL and Crossman RR. Drug-induced QT prolongation. *US Pharm*. 2007;32(2):44-50.
- United States Department of Health and Human Services (HHS). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. 2009 [cited 30 Jan 2014]. Available from: [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE\\_4.02\\_2009-09-15\\_QuickReference\\_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf).
- United States Department of Health and Human Services (HHS), Food and Drug Administration, Center for Drug Evaluation and Research. Draft guidance. Drug interaction studies – Study design, data analysis, implications for dosing, and labeling recommendations. February 2012 [cited 04 Feb 2014]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/u cm292362.pdf>.

## 20. APPENDICES

### 20.1. Drugs Associated with QT Prolongation

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Ketoconazole	Venlafaxine		
	Itraconazole			

Reference: [Thompson and Crossman, 2007](#)

## 20.2. Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Reference: [Oken et al, 1982](#)



**Summary of Protocol Changes**

**Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer**

Previous Version: Version 3.0, dated 17 Mar 2015

Current Version: Version 4.1, dated 11 Sept 2015

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Global	N/A	Minor grammatical, typographical, and/or formatting/style errors and inconsistencies were corrected, including (but not limited to): replacing spelled numbers with numerals, adding articles before abbreviations, adding/removing hyphens, updating list of abbreviations, adjusting spacing after periods	Editorial changes were made throughout to improve clarity and flow, as well as maintain a consistent style.
Global	N/A	Various unsubstantial changes were made, ie, those which are unlikely to have a significant impact on the safety, physical, or mental integrity of the subjects; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of the investigational product.	Provide increased clarity to the study protocol. These changes will be documented in detail in the redline version of the final protocol.
Synopsis, Methods Investigational Plan, Overall study design	<del>Participation in Part 2 of the study may extend beyond Day 22 if the amount of radioactivity found in the Day 22 urine or fecal samples is higher than 0.1% of the dose given.</del>	Participation in Part 2 of the study may extend beyond Day 21 <u>based on</u> <u>the amount of radioactivity recovered.</u>	Modification made to reflect changes to urine/fecal collection stop criteria, which were modified per site request to account for the amount of radioactivity likely to be recovered.
Synopsis, Methods Investigational Plan, Overall study design	At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments.	At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments.	Modification made to account for note to file dated 1 June 2015

Niraparib  
Protocol PR-30-5015-C Amendment 3 Summary of Changes

TESARO, Inc.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	once a day (QD) and will undergo safety assessments and <del>PK</del> blood sampling.		
Synopsis, Methods Investigational Plan, Overall study design	Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [+3] days) to receive study drug and for safety assessments, <del>PK</del> blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment.	Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [+3] days) to receive study drug and for safety assessments, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment.	Modification made to account for note to file dated 1 June 2015
Synopsis, Methods Investigational Plan, Overall study design	At end of treatment (EOT), safety assessments, <del>PK</del> blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.	At end of treatment (EOT), safety assessments, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.	Modification made to account for note to file dated 1 June 2015
Synopsis, Inclusion Criteria Inclusion Criteria	Platelets $\geq 100,000/\mu\text{L}$	Platelets $\geq 150,000/\mu\text{L}$	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, Inclusion Criteria	N/A	<u>Subject must agree to blood samples during screening and at the end of treatment for cytogenetic analysis.</u>	This change was made to provide guidance on monitoring and following patients due

Niraparib  
Protocol PR-30-5015-C Amendment 3 Summary of Changes

TESARO, Inc.

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
Inclusion Criteria			to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, Exclusion Criteria Exclusion Criteria	Subject has a <del>baseline</del> corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.	Subject has a corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.	Edited for clarity.
Synopsis, exclusion criteria Exclusion criteria	N/A	<u>Subject has any known, persistent (&gt;4 weeks) ≥Grade 3 hematological toxicity or fatigue from prior cancer therapy.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, exclusion criteria Exclusion criteria	Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.	Subject has a history or current evidence of any condition, therapy, or laboratory abnormality ( <u>including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]</u> ) that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, exclusion criteria Exclusion criteria	N/A	<u>Subject has any known history of myelodysplastic syndrome (MDS) or a pre-treatment cytogenetic testing result at risk for a diagnosis of MDS/acute myeloid leukemia (AML).</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

# Niraparib Protocol PR-30-5015-C Amendment 3 Summary of Changes

TESARO, Inc.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		<p><u>aspirate/biopsy findings (which must include a classification according to WHO criteria (Vardiman 2009) and other sample testing results related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the subject's study file.</u></p> <p><u>Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the patient develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Laboratory Manual.</u></p> <p><u>FISH, MDS test result must be negative for cytogenetic abnormalities commonly observed in myeloid malignancies. The FISH, MDS result must be received prior to randomization.</u></p>	
SOA Part 2	N/A	<u>Blood sample for cytogenetic analysis only if patient discontinues.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
SOA Extension	N/A	<u>New malignancy information will be collected for all patients via telephone every 90 days following the treatment discontinuation visit (subjects in the extension study only). See <a href="#">Section 8.1.12</a>.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Introduction, Phase 1 Studies	<del>As of 15 November 2013, 144 subjects have been treated with oral niraparib at doses up to 400 mg QD in Phase 1 studies, and treatment with niraparib has been generally well tolerated.</del>	<u>Treatment with niraparib has been generally well-tolerated. Refer to the Investigator's Brochure for more information.</u>	Modification made to minimize historical discrepancies with current version of IB
Introduction, Phase 1 Studies	The most commonly reported (>5.0%) adverse	The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were fatigue, nausea, anemia, constipation,	Modification made to minimize historical discrepancies with current version of IB

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>events (AEs; all grades) in the clinic were (n=144): fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), rash (10.4%), dizziness (9.7%), electrocardiogram (ECG) QT prolonged (9.7%), pyrexia (9.7%), abdominal distension (9.0%), urinary tract infection (9.0%), weight decreased (9.0%);</p>	<p>thrombocytopenia, vomiting, decreased appetite, neutropenia, headache, diarrhea, dyspnea, cough, leukopenia, hyponatremia, back pain, hyperglycemia, insomnia, abdominal pain, hypokalemia, blood alkaline phosphatase increased, pain in extremity, hypertension, peripheral edema, rash, dizziness, electrocardiogram (ECG) QT prolonged, pyrexia, abdominal distension, urinary tract infection, weight decreased, abdominal pain lower, alopecia, neoplasm malignant, dry mouth, hypoalbuminemia, musculoskeletal pain, stomatitis, arthralgia, blood creatinine increase, chills, dyspepsia, hypomagnesemia, paresthesia, aspartate aminotransferase increased, dehydration, musculoskeletal chest pain, neck pain, alanine aminotransferase (ALT) increased, dysgeusia, myalgia, and palpitations.</p>	

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>abdominal pain lower (8.3%), alopecia (8.3%), neoplasm malignant (8.3%), dry mouth (7.6%), hypoalbuminemia (7.6%), musculoskeletal pain (7.6%), stomatitis (7.6%), arthralgia (6.9%), blood creatinine increase (6.9%), chills (6.9%), dyspepsia (6.9%), hypomagnesemia (6.9%), paresthesia (6.9%), aspartate aminotransferase (AST) increased (6.3%), dehydration (6.3%), musculoskeletal chest pain (6.3%), neck pain (6.3%), alanine aminotransferase (ALT) increased (5.6%), dysgeusia (5.6%), myalgia (5.6%), and palpitations (5.6%).</p>		
Introduction, Phase 1 Studies	<p>The most commonly reported drug-related (&gt;5.0%) AEs (all grades) in the clinic were (<math>n=129</math>): fatigue (45.1%), nausea (42.4%), anemia (41.0%), thrombocytopenia (32.6%), decreased appetite (23.6%),</p>	<p>The most commonly reported drug-related (&gt;5.0%) AEs (all grades) in the clinic were: fatigue, nausea, anemia, thrombocytopenia, decreased appetite, neutropenia, vomiting, constipation, leukopenia, diarrhea, insomnia, dyspnea, ECG QT prolonged, headache, stomatitis, hyponatremia, and alopecia.</p>	<p>Modification made to minimize historical discrepancies with current version of IB</p>

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	neutropenia (22.2%), vomiting (22.2%), constipation (19.4%), leukopenia (18.1%), diarrhea (10.4%), insomnia (8.3%), dyspnea (6.9%), ECG QT prolonged (6.9%), headache (6.3%), stomatitis (6.3%), hyponatremia (5.6%), and alopecia (5.6%).		
Introduction, Study PN001	<p>The maximum tolerated dose (MTD) of niraparib dosed orally QD was determined to be 300 mg in subjects with advanced solid tumors or hematologic malignancies. The dose-limiting toxicity for niraparib is thrombocytopenia, with Grade 4 thrombocytopenia reported in 2 of 6 subjects treated at the 400 mg dose level. For the 44 subjects treated at the MTD, 21 subjects experienced thrombocytopenia, 16 subjects experienced neutropenia, and 34 subjects experienced</p>	N/A (deleted all)	Modification made to minimize historical discrepancies with current version of IB

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>anemia. During routine safety monitoring, 12 of 104 subjects reported AEs of prolonged QTc (6 subjects experienced a Grade 1 event, 5 subjects experienced a Grade 2 event, and 1 subject experienced a Grade 3 event). Preliminary evaluation showed 8 of these subjects (7.7%) had QT prolongation that was assessed as at least possibly related to study drug. Of these 8 subjects, 7 received 300 mg of niraparib QD and 1 received 210 mg of niraparib QD. A total of 8 subjects exceeded a 30 msec change from baseline during the study, with the maximum being 70 msec. Given that these were spontaneous reports, and not part of a controlled QTc evaluation, it would be difficult to assess the relationship to niraparib. Until a more rigorous evaluation of QTc can be conducted, subjects should be evaluated for</p>		

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
	<p>QTc prolongation.  A preliminary analysis of plasma drug concentration profiles indicated that the maximum observed plasma concentration (<math>C_{max}</math>) after oral dosing occurred at approximately 3 hours. There was an approximate 3 to 4 fold accumulation in the area under the plasma concentration time curve (AUC), <math>C_{max}</math>, and plasma concentration at 24 hours postdose from Cycle 1/Day 1 to Cycle 2/Day 1. Mean apparent terminal half life (<math>t_{1/2}</math>) ranged from 32.8 to 46.0 hours over the 60 to 400 mg dose range. PK parameters appeared to be dose proportional. Although efficacy was not the primary objective for this Phase 1 study, antitumor activity was observed in subjects taking niraparib as monotherapy at oral dose levels ranging from 60 to 400 mg. Based on Investigator evaluation using Response</p>		

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or cancer antigen 125 (CA-125) criteria, an overall response rate of 13% was observed for all subjects in this study. Analysis of the 20 <i>BRCA1</i> mutant ovarian cancer subjects enrolled in the study demonstrated that this group showed a 35% overall response rate according to RECIST version 1.1 and/or CA-125 criteria.</p>		
Introduction, Phase 3 Studies	<p>The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline <i>BRCA</i> mutation breast cancer subjects (PR-30-5010-C; BRAVO) and to platinum-sensitive ovarian cancer subjects (PR-30-5011-C; NOVA). A total of 55 subjects had been randomized in the Phase 3 clinical study program as of 07 January 2014. Preliminary results</p>	<p>The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline <i>BRCA</i> mutation breast cancer subjects (<a href="#">PR-30-5010-C; BRAVO</a>) and to platinum-sensitive ovarian cancer subjects (<a href="#">PR-30-5011-C; NOVA</a>). <u>Treatment with niraparib has been generally well tolerated. Refer to the Investigator's Brochure for more information.</u></p>	Modification made to minimize historical discrepancies with current version of IB

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
	<del>from 15 subjects who completed the PR-30-5011-C study suggest administration of niraparib with food is expected to have a negligible effect on the PK of niraparib. Of the 16 subjects enrolled in the PR-30-5011-C study as of 15 November 2013, the most commonly reported AEs were gastrointestinal disorders (constipation, nausea, and vomiting) and metabolism and nutrition disorders (decreased appetite).</del>		
Introduction, Risks and Benefits	N/A	Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in <a href="#">Section 3.4</a> and <a href="#">Section 8.1.8</a> .	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Dose Adjustment Criteria, <a href="#">Table 6</a>	Hemoglobin $\leq 8$ g/dL	Hemoglobin <u><math>\leq 8</math></u> g/dL	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Dose Adjustment Criteria	N/A	<u>Any subject requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed. The subject must be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, then the subject must permanently discontinue study treatment.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Restrictions During Study	<p>Subjects should try to minimize their exposure to ultraviolet light, including natural or artificial sunlight (tanning beds or ultraviolet A or B treatment), while taking niraparib to avoid any possibility of phototoxicity. If subjects need to be outdoors while taking niraparib, they should wear loose fitting clothes and hats that protect skin from direct sun exposure and discuss other sun protection measures with their physician, such as ultraviolet protection sunscreen. If a sunburn-like reaction or skin eruption occurs, subjects should contact their physician.</p>	<u>N/A (deleted)</u>	The in vivo phototoxicity study is complete and was negative.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Restrictions During Study	N/A	<u>Subjects are not to take medications known to prolong QTc (Section 16.1) while participating in the study.</u>	This change was made to clarify that patients also may not take QTc-prolonging medications during the trial (in addition to these meds being exclusionary to enter the trial).
Prior and Concomitant medications	N/A	<u>Subjects must not be receiving medications that prolong QTc at Screening and for the duration of the study (Section 16.1)</u>	This change was made to clarify that patients also may not take QTc-prolonging medications during the trial (in addition to these meds being exclusionary to enter the trial).
Study Drug Packaging and Labeling	N/A	<u>The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-subject-specific.</u>	The packaging, labeling, and storage language was updated for consistency with the current protocol template and other protocols in the niraparib development program.
Study Drug Storage	<del>The 100 mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 15°C to 25°C. Until study drug is dispensed to the subjects, the study drug will be stored in a suitable container, at storage conditions specified by the Sponsor, in a securely locked area, accessible to authorized personnel only.</del>	<u>All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed to the subjects, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.</u>	The packaging, labeling, and storage language was updated for consistency with the current protocol template and other protocols in the niraparib development program.
Pharmacokinetic Assessments: Blood sample	<del>For the extension study, blood samples will be collected for PK analysis</del>	N/A (deleted)	Modification made to account for note to file dated 01 June 2015

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
collection	<p>at the following times:</p> <p>Cycle 1/Day 1 Visit (within 30 min predose and 2 hours <math>\pm</math>15 min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours <math>\pm</math>15 min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).</p>		
Pharmacokinetic Assessments, Urine sample collection	<p>If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.</p>	<p>When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. <u>The discontinuation of urine sample collections will be based on:</u></p> <ol style="list-style-type: none"> <li data-bbox="734 866 1474 992">1. <u>If the total radioactivity in the Day 14 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity <math>\leq</math>85% (feces and urine), then urine samples will be collected every 24 hours through Day 21.</u></li> <li data-bbox="734 992 1474 1117">2. <u>If the total radioactivity in the Day 21 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity <math>\leq</math>85% (feces and urine), then urine samples will continue to be collected every 24 hours.</u></li> <li data-bbox="734 1117 1474 1302">3. <u>Urine sample collection will stop at the end of Day 21 if the recovered radioactivity is <math>&lt;</math> 1% (per 24 hours) for the 2 consecutive days prior to Day 21 (Days 19 and 20). If this is not the case, then collection will stop as soon as the recovered radioactivity is <math>&lt;</math> 1% (per 24 hours) for 2 consecutive days after Day 21.</u></li> </ol>	<p>Changes made to urine/fecal collection stop criteria per site request to account for the amount of radioactivity likely to be recovered.</p>

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Pharmacokinetic Assessments, Urine sample collection, <a href="#">Table 10</a>	<p>If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.</p>	<p>See above for collection stop criteria.</p>	<p>Changes made to urine/fecal collection stop criteria per site request to account for the amount of radioactivity likely to be recovered.</p>
Pharmacokinetic Assessments, Fecal sample collection	<p>If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the</p>	<p>The discontinuation of fecal sample collections will be based on:</p> <ol style="list-style-type: none"> <li data-bbox="734 1090 1474 1204">1. If the total radioactivity in the Day 14 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity &lt;85% (feces and urine), then fecal samples will be collected every 24 hours through Day 21.</li> <li data-bbox="734 1212 1474 1326">2. If the total radioactivity in the Day 21 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity &lt;85% (feces and urine), then fecal samples will continue to be collected every 24 hours.</li> <li data-bbox="734 1334 1474 1416">3. Feces sample collection will stop at the end of day Day 21 if the recovered radioactivity is &lt; 1% (per 24 hours) for the two consecutive days prior to Day 21 (Days 19 and 20). If this is not</li> </ol>	<p>Changes made to urine/fecal collection stop criteria per site request to account for the amount of radioactivity likely to be recovered.</p>

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.</p>	<p><u>the case, then collection will stop as soon as the recovered radioactivity is &lt; 1% (per 24 hours) for two consecutive days after Day 21.</u></p>	
<p>Pharmacokinetic Assessments, Fecal sample collection, <a href="#">Table 11</a></p>	<p>If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.</p>	<p><u>See above for collection stop criteria</u></p>	<p>Changes made to urine/fecal collection stop criteria per site request to account for the amount of radioactivity likely to be recovered.</p>

Niraparib  
Protocol PR-30-5015-C Amendment 3 Summary of Changes

TESARO, Inc.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
Synopsis, Criteria for Evaluation, Pharmacokinetics; Pharmacokinetic Assessments, Sample analysis	<del>Extension study: Plasma niraparib concentrations will be used to determine the following PK parameters: <math>C_{max}</math>, <math>T_{max}</math>, <math>AUC_{0\text{-last}}</math>, <math>AUC_{0\text{-inf}}</math>, and <math>t_{1/2}</math>.</del>	N/A (deleted)	Modification made to account for note to file dated 01 June 2015
Assessments of Safety, Safety parameters, clinical laboratory assessments	N/A	<u>For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization (WHO) criteria (Vardiman 2009) and other sample testing reports related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the subject's study file.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Assessments of Safety, Safety Parameters, (new sections)	N/A	<u>Blood and Tissue Samples</u> <u>Whole blood samples will be collected for all subjects during screening and at EOT. Some samples will be used to determine eligibility per MDS/AML-related criteria (see Section 4). These test results must be received prior to randomization. For all eligible subjects, remaining samples will be stored. Stored samples will be evaluated for mutations of selected myeloid-associated genes if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). Details on blood and tissue sample collection can be found in the Laboratory Manual.</u> <u>New Malignancies</u> <u>Although overall survival is not an endpoint in this study, to monitor for MDS/AML and the occurrence of new malignancies, new malignancy information will be collected for all subjects via telephone every 90 days following the treatment discontinuation visit (subjects in the extension</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		<u>study only).</u>	
Adverse and Serious Adverse Events, Definition of Adverse Events	N/A (new section)	The event of disease progression is an efficacy criterion and is therefore <u>not considered an AE. If AEs/SAEs occur in relation to disease progression, then the AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 8.6.</u>	This change incorporates into the protocol an administrative letter that was issued on 06 Mar 2015 clarifying that disease progression alone is not considered an adverse event and that events occurring in relation to progression that meet the adverse event reporting criteria should be reported as noted in the relevant sections of the study protocol.
Adverse and Serious Adverse Events, Definition of Serious Adverse Events	Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE;	Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, <u>disease progression</u> , etc.) will not be considered an SAE	This change incorporates into the protocol an administrative letter that was issued on 06 Mar 2015 clarifying that disease progression alone is not considered an adverse event and that events occurring in relation to progression that meet the adverse event reporting criteria should be reported as noted in the relevant sections of the study protocol.
Adverse Events and Serious Adverse Events, Recording of Adverse Events	AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New AEs and SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see <a href="#">Table 1</a> , <a href="#">Table 2</a> , and <a href="#">Table 3</a> for schedules of events).	AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New <u>AEs and SAEs</u> (including deaths) will be collected for 30 days after treatment discontinuation (see Table 1, Table 2, and Table 3 for schedules of events) <u>or until new anticancer therapy is initiated.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
N/A (new section)	N/A (new section)	<u>Post-treatment Analyses</u> <u>Descriptive summary statistics will be used to summarize post study treatment data (ie, any new malignancy). In addition, the relationship between cytogenetic abnormalities and safety parameters may be</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale																																																							
		<u>explored.</u>																																																								
Synopsis, Criteria for Evaluation, Pharmacokinetics; Statistics, Pharmacokinetic Analysis, Extension Study	<del>Extension Study Plasma concentrations of niraparib based on MS ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics.</del>	N/A (deleted)	Modification made to account for note to file dated 01 June 2015																																																							
<b>Table 12</b>	<b>PREVIOUS:</b> <b>Drugs Associated with QT Prolongation</b> <b>Table 1: Drugs Associated with QT prolongation</b>	<table border="1"> <thead> <tr> <th>Antiarrhythmics</th><th>Antimicrobials</th><th>Antidepressants</th><th>Antipsychotics</th><th>Others (including Selected Antiemetics)</th></tr> </thead> <tbody> <tr><td>Amiodarone</td><td>Levofloxacin</td><td>Amitriptyline</td><td>Haloperidol</td><td>Cisapride</td></tr> <tr><td>Sotalol</td><td>Ciprofloxacin</td><td>Desipramine</td><td>Droperidol</td><td>Sumatriptan</td></tr> <tr><td>Quinidine</td><td>Gatifloxacin</td><td>Imipramine</td><td>Quetiapine</td><td>Zolmitriptan</td></tr> <tr><td>Procainamide</td><td>Moxifloxacin</td><td>Doxepin</td><td>Thioridazine</td><td>Arsenic</td></tr> <tr><td>Dofetilide</td><td>Clarithromycin</td><td>Fluoxetine</td><td>Ziprasidone</td><td>Dolasetron</td></tr> <tr><td>Ibutilide</td><td>Erythromycin</td><td>Sertraline</td><td></td><td>Methadone</td></tr> <tr><td></td><td>Itraconazole</td><td>Venlafaxine</td><td></td><td>Metoclopramide</td></tr> <tr><td></td><td>Azithromycin</td><td></td><td></td><td>Domperidone</td></tr> <tr><td></td><td></td><td></td><td></td><td>Ondansetron</td></tr> <tr><td></td><td></td><td></td><td></td><td>Diphenhydramine</td></tr> </tbody> </table>	Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)	Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride	Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan	Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan	Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic	Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron	Ibutilide	Erythromycin	Sertraline		Methadone		Itraconazole	Venlafaxine		Metoclopramide		Azithromycin			Domperidone					Ondansetron					Diphenhydramine	This table was updated to refine list based on potential to cause QT prolongation, Torsades de Pointes, or drug-drug interaction; references were reformatted for consistency with other reference presentation in the document.
Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)																																																						
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride																																																						
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	Itraconazole	Venlafaxine		Metoclopramide																																																						
	Azithromycin			Domperidone																																																						
				Ondansetron																																																						
				Diphenhydramine																																																						
<b>REVISED:</b> <b>Drugs Associated with Torsades de Pointes (TdP)</b> <b>Table 2: Drugs Associated with QT prolongation and TdP</b>																																																										

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )		Revised and/or Updated text (added text shown by <u>underline</u> )			Rationale
	<b>Antiarrhythmics</b>	<b>Antimicrobials</b>	<b>Antidepressants</b>	<b>Antipsychotics</b>	<b>Others (including Selected Antiemetics)</b>	
	Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride	
	Sotalol	Ciprofloxacin	Doxepin	Droperidol	Sumatriptan	
	Quinidine	Gatifloxacin		Quetiapine	Zolmitriptan	
	Procainamide	Moxifloxacin		Thioridazine	Arsenic	
	Dofetilide	Clarithromycin		Ziprasidone	Dolasetron	
	Ibutilide	Erythromycin			Methadone	
		Ketoconazole*				
		Itraconazole				

\*Topical use allowed for ketoconazole  
Cardiac Risk in the Young sponsored web site on Sudden Arrhythmic Death Syndrome.  
Available at:



**Summary of Protocol Changes**

**Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer**

Previous Version: Version 3.0, dated 17 Mar 2015

Current Version: Version 4.0, dated 11 Sept 2015

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Global	N/A	Minor grammatical, typographical, and/or formatting/style errors and inconsistencies were corrected, including (but not limited to): replacing spelled numbers with numerals, adding articles before abbreviations, adding/removing hyphens, updating list of abbreviations, adjusting spacing after periods	Editorial changes were made throughout to improve clarity and flow, as well as maintain a consistent style.
Global	N/A	Various unsubstantial changes were made, ie, those which are unlikely to have a significant impact on the safety, physical, or mental integrity of the subjects; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of the investigational product.	Provide increased clarity to the study protocol. These changes will be documented in detail in the redline version of the final protocol.
Synopsis, Methods Investigational Plan, Overall study design	<del>Participation in Part 2 of the study may extend beyond Day 22 if the amount of radioactivity found in the Day 22 urine or fecal samples is higher than 0.1% of the dose given.</del>	Participation in Part 2 of the study may extend beyond Day 21 <u>based on</u> <u>the amount of radioactivity recovered.</u>	Modification made to reflect changes to urine/fecal collection stop criteria, which were modified per site request to account for the amount of radioactivity likely to be recovered.
Synopsis, Methods Investigational Plan, Overall study design	At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments.	At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100-mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments.	Modification made to account for note to file dated 1 June 2015

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Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	once a day (QD) and will undergo safety assessments and <del>PK</del> blood sampling.		
Synopsis, Methods Investigational Plan, Overall study design	Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [+3] days) to receive study drug and for safety assessments, <del>PK</del> blood sampling, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment.	Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [+3] days) to receive study drug and for safety assessments, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment.	Modification made to account for note to file dated 1 June 2015
Synopsis, Methods Investigational Plan, Overall study design	At end of treatment (EOT), safety assessments, <del>PK</del> blood sampling, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.	At end of treatment (EOT), safety assessments, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.	Modification made to account for note to file dated 1 June 2015
Synopsis, Inclusion Criteria Inclusion Criteria	Platelets $\geq 100,000/\mu\text{L}$	Platelets $\geq 150,000/\mu\text{L}$	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, Inclusion Criteria	N/A	<u>Subject must agree to blood samples during screening and at the end of treatment for cytogenetic analysis.</u>	This change was made to provide guidance on monitoring and following patients due

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Inclusion Criteria			to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, Inclusion Criteria Inclusion Criteria	Subject has a <del>baseline</del> corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.	Subject has a corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.	Edited for clarity.
Synopsis, exclusion criteria Exclusion criteria	N/A	<u>Subject has any known, persistent (&gt;4 weeks) ≥Grade 3 hematological toxicity or fatigue from prior cancer therapy.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, exclusion criteria Exclusion criteria	Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.	Subject has a history or current evidence of any condition, therapy, or laboratory abnormality ( <u>including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]</u> ) that might confound the results of the study, interfere with the subject's participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Synopsis, exclusion criteria Exclusion criteria	N/A	<u>Subject has any known history of myelodysplastic syndrome (MDS) or a pre-treatment cytogenetic testing result at risk for a diagnosis of MDS/acute myeloid leukemia (AML).</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

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Synopsis, exclusion criteria, Exclusion criteria	Subject is receiving concomitant medication(s) that prolong QTc (Appendix 16.2).	Subject is receiving concomitant medications that prolong QTc <u>and is unable to discontinue use for the duration of the study</u> ( <a href="#">Appendix 16.2</a> ).												This change was made to clarify that patients also may not take QTc-prolonging medications during the trial (in addition to these meds being exclusionary to enter the trial).
SOA Part 1, Part 2, Extension study	New serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit.	New <u>adverse events (AEs)</u> and serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit, <u>or until new anticancer therapy is initiated</u> .												This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
SOA Part 2	N/A	<u>Bone marrow aspirate and biopsy sample collection (whole blood) for cytogenetic analysis<sup>a</sup></u>											X	These changes were made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
		<u>Whole blood samples for cytogenetic analysis</u>	X <sup>b</sup>										X <sup>c</sup>	
		<u>Whole blood sample for FISH, MDS</u>	X <sup>d</sup>											
SOA Part 2, Extension	N/A	<u>For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the local hematologist's report of</u>												This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		<p><u>aspirate/biopsy findings (which must include a classification according to WHO criteria (Vardiman 2009) and other sample testing results related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the subject's study file.</u></p> <p><u>Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the patient develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Laboratory Manual.</u></p> <p><u>Blood sample for cytogenetic analysis only if patient discontinues. FISH, MDS test result must be negative for cytogenetic abnormalities commonly observed in myeloid malignancies. The FISH, MDS result must be received prior to randomization.</u></p>	
SOA Extension	N/A	<p><u>New malignancy information will be collected for all patients via telephone every 90 days following the treatment discontinuation visit (subjects in the extension study only). See <a href="#">Section 8.1.12</a></u></p>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Introduction, Phase 1 Studies	<del>As of 15 November 2013, 144 subjects have been treated with oral niraparib at doses up to 400 mg QD in Phase 1 studies, and treatment with niraparib has been generally well tolerated.</del>	<p><u>Treatment with niraparib has been generally well-tolerated. Refer to the Investigator's Brochure for more information.</u></p>	Modification made to minimize historical discrepancies with current version of IB
Introduction, Phase 1 Studies	The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were (n=144): fatigue (58.3%),	The most commonly reported (>5.0%) adverse events (AEs; all grades) in the clinic were fatigue, nausea, anemia, constipation, thrombocytopenia, vomiting, decreased appetite, neutropenia, headache, diarrhea, dyspnea, cough, leukopenia, hyponatremia, back pain, hyperglycemia, insomnia, abdominal pain, hypokalemia, blood alkaline	Modification made to minimize historical discrepancies with current version of IB

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), leukopenia (20.8%), hyponatremia (19.4%), back pain (17.4%), hyperglycemia (16.0%), insomnia (16.0%), abdominal pain (13.9%), hypokalemia (13.2%), blood alkaline phosphatase increased (11.1%), pain in extremity (11.1%), hypertension (10.4%), peripheral edema (10.4%), rash (10.4%), dizziness (9.7%), electrocardiogram (ECG) QT prolonged (9.7%), pyrexia (9.7%), abdominal distension (9.0%), urinary tract infection (9.0%), weight decreased (9.0%), abdominal pain lower (8.3%), alopecia (8.3%), neoplasm malignant</p>	<p>phosphatase increased, pain in extremity, hypertension, peripheral edema, rash, dizziness, electrocardiogram (ECG) QT prolonged, pyrexia, abdominal distension, urinary tract infection, weight decreased, abdominal pain lower, alopecia, neoplasm malignant, dry mouth, hypoalbuminemia, musculoskeletal pain, stomatitis, arthralgia, blood creatinine increase, chills, dyspepsia, hypomagnesemia, paresthesia, aspartate aminotransferase increased, dehydration, musculoskeletal chest pain, neck pain, alanine aminotransferase (ALT) increased, dysgeusia, myalgia, and palpitations.</p>	

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
	<p>(8.3%), dry mouth (7.6%), hypoalbuminemia (7.6%), musculoskeletal pain (7.6%), stomatitis (7.6%), arthralgia (6.9%), blood creatinine increase (6.9%), chills (6.9%), dyspepsia (6.9%), hypomagnesemia (6.9%), paresthesia (6.9%), aspartate aminotransferase (AST) increased (6.3%), dehydration (6.3%), musculoskeletal chest pain (6.3%), neck pain (6.3%), alanine aminotransferase (ALT) increased (5.6%), dysgeusia (5.6%), myalgia (5.6%), and palpitations (5.6%).</p>		
Introduction, Phase 1 Studies	<p>The most commonly reported drug-related (&gt;5.0%) AEs (all grades) in the clinic were (<u>n=129</u>): fatigue (45.1%), nausea (42.4%), anemia (41.0%), thrombocytopenia (32.6%), decreased appetite (23.6%), neutropenia (22.2%), vomiting (22.2%), constipation (19.4%),</p>	<p>The most commonly reported drug-related (&gt;5.0%) AEs (all grades) in the clinic were: fatigue, nausea, anemia, thrombocytopenia, decreased appetite, neutropenia, vomiting, constipation, leukopenia, diarrhea, insomnia, dyspnea, ECG QT prolonged, headache, stomatitis, hyponatremia, and alopecia.</p>	<p>Modification made to minimize historical discrepancies with current version of IB</p>

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	leukopenia (18.1%), diarrhea (10.4%), insomnia (8.3%), dyspnea (6.9%), ECG QT prolonged (6.9%), headache (6.3%), stomatitis (6.3%), hyponatremia (5.6%), and alopecia (5.6%).		
Introduction, Study PN001	The maximum tolerated dose (MTD) of niraparib dosed orally QD was determined to be 300 mg in subjects with advanced solid tumors or hematologic malignancies. The dose-limiting toxicity for niraparib is thrombocytopenia, with Grade 4 thrombocytopenia reported in 2 of 6 subjects treated at the 400 mg dose level. For the 44 subjects treated at the MTD, 21 subjects experienced thrombocytopenia, 16 subjects experienced neutropenia, and 34 subjects experienced anemia. During routine safety monitoring, 12 of 104	N/A (deleted all)	Modification made to minimize historical discrepancies with current version of IB

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>subjects reported AEs of prolonged QTc (6 subjects experienced a Grade 1 event, 5 subjects experienced a Grade 2 event, and 1 subject experienced a Grade 3 event). Preliminary evaluation showed 8 of these subjects (7.7%) had QT prolongation that was assessed as at least possibly related to study drug. Of these 8 subjects, 7 received 300 mg of niraparib QD and 1 received 210 mg of niraparib QD. A total of 8 subjects exceeded a 30 msec change from baseline during the study, with the maximum being 70 msec. Given that these were spontaneous reports, and not part of a controlled QTc evaluation, it would be difficult to assess the relationship to niraparib. Until a more rigorous evaluation of QTc can be conducted, subjects should be evaluated for QTc prolongation. A preliminary analysis of plasma drug</p>		

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>concentration profiles indicated that the maximum observed plasma concentration (<math>C_{max}</math>) after oral dosing occurred at approximately 3 hours. There was an approximate 3- to 4-fold accumulation in the area under the plasma concentration time curve (AUC), <math>C_{max}</math>, and plasma concentration at 24 hours postdose from Cycle 1/Day 1 to Cycle 2/Day 1. Mean apparent terminal half-life (<math>t_{1/2}</math>) ranged from 32.8 to 46.0 hours over the 60- to 400-mg dose range. PK parameters appeared to be dose proportional. Although efficacy was not the primary objective for this Phase 1 study, antitumor activity was observed in subjects taking niraparib as monotherapy at oral dose levels ranging from 60 to 400 mg. Based on Investigator evaluation using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or cancer</p>		

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	<p>antigen 125 (CA-125) criteria, an overall response rate of 13% was observed for all subjects in this study. Analysis of the 20 <i>BRCA</i> mutant ovarian cancer subjects enrolled in the study demonstrated that this group showed a 35% overall response rate according to RECIST version 1.1 and/or CA-125 criteria.</p>		
Introduction, Phase 3 Studies	<p>The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline <i>BRCA</i> mutation breast cancer subjects (PR-30-5010-C; BRAVO) and to platinum-sensitive ovarian cancer subjects (PR-30-5011-C; NOVA). A total of 55 subjects had been randomized in the Phase 3 clinical study program as of 07 January 2014. Preliminary results from 15 subjects who completed the PR-30-5011-C study</p>	<p>The 300-mg daily dose of niraparib is currently being administered in two Phase 3 studies to previously treated, human epidermal growth factor 2 (HER2) negative, germline <i>BRCA</i> mutation breast cancer subjects (PR-30-5010-C; BRAVO) and to platinum-sensitive ovarian cancer subjects (PR-30-5011-C; NOVA). <u>Treatment with niraparib has been generally well-tolerated. Refer to the Investigator's Brochure for more information.</u></p>	<p>Modification made to minimize historical discrepancies with current version of IB</p>

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
	suggest administration of niraparib with food is expected to have a negligible effect on the PK of niraparib. Of the 16 subjects enrolled in the PR-30-5011 C study as of 15 November 2013, the most commonly reported AEs were gastrointestinal disorders (constipation, nausea, and vomiting) and metabolism and nutrition disorders (decreased appetite).		
Introduction, Risks and Benefits	N/A	Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in <a href="#">Section 3.4</a> and <a href="#">Section 8.1.8</a> .	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Dose Adjustment Criteria, Table 6	Hemoglobin $\leq 8$ g/dL	Hemoglobin <u><math>\leq 8</math></u> g/dL	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Dose Adjustment Criteria	N/A	<u>Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed. The patient must be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less within 4 weeks. If a diagnosis of MDS/AML is confirmed by a</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		<u>hematologist, the patient must permanently discontinue study treatment.</u>	
Restrictions During Study	<del>Subjects should try to minimize their exposure to ultraviolet light, including natural or artificial sunlight (tanning beds or ultraviolet A or B treatment), while taking niraparib to avoid any possibility of phototoxicity. If subjects need to be outdoors while taking niraparib, they should wear loose fitting clothes and hats that protect skin from direct sun exposure and discuss other sun protection measures with their physician, such as ultraviolet protection sunscreen. If a sunburn-like reaction or skin eruption occurs, subjects should contact their physician.</del>	N/A (deleted)	The in vivo phototoxicity study is complete and was negative.
Restrictions During Study	N/A	Subjects are not to take medications known to prolong QTc ( <a href="#">Section 16.1</a> ) while participating in the study.	This change was made to clarify that patients also may not take QTc-prolonging

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
			medications during the trial (in addition to these meds being exclusionary to enter the trial).
Prior and Concomitant medications	N/A	<u>Patients must not be receiving medications that prolong QTc at Screening and for the duration of the study (Section 16.1)</u>	This change was made to clarify that patients also may not take QTc-prolonging medications during the trial (in addition to these meds being exclusionary to enter the trial).
Study Drug Packaging and Labeling	N/A	<u>The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-patient-specific.</u>	The packaging, labeling, and storage language was updated for consistency with the current protocol template and other protocols in the niraparib development program.
Study Drug Storage	<del>The 100 mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 15°C to 25°C. Until study drug is dispensed to the subjects, the study drug will be stored in a suitable container, at storage conditions specified by the Sponsor, in a securely locked area, accessible to authorized personnel only.</del>	<u>All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.</u>	The packaging, labeling, and storage language was updated for consistency with the current protocol template and other protocols in the niraparib development program.
Pharmacokinetic Assessments: Blood sample collection	<del>For the extension study, blood samples will be collected for PK analysis at the following times: Cycle 1/Day 1 Visit</del>	N/A (deleted)	Modification made to account for note to file dated 01 June 2015

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
	(within 30 min predose and 2 hours $\pm$ 15 min postdose), Cycle 2/Day 1 Visit (within 30 min predose and 2 hours $\pm$ 15 min postdose), Cycle 4/Day 1 Visit (within 30 min predose), and Cycle 8/Day 1 Visit (within 30 min predose).		
Pharmacokinetic Assessments, Urine sample collection	If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.	<p>When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. <u>The discontinuation of urine sample collections will be based on:</u></p> <ol style="list-style-type: none"> <li>1. <u>If the total radioactivity in the Day 14 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity <math>\leq</math>85% (feces and urine), then urine samples will be collected every 24 hours through Day 21.</u></li> <li>2. <u>If the total radioactivity in the Day 21 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity <math>\leq</math>85% (feces and urine), then urine samples will continue to be collected every 24 hours.</u></li> <li>3. <u>Urine sample collection will stop at the end of Day 21 if the recovered radioactivity is <math>&lt;</math> 1% (per 24 hours) for the 2 consecutive days prior to Day 21 (Days 19 and 20). If this is not the case, then collection will stop as soon as the recovered radioactivity is <math>&lt;</math> 1% (per 24 hours) for 2 consecutive days after Day 21.</u></li> </ol>	Changes made to urine/fecal collection stop criteria per site request to account for the amount of radioactivity likely to be recovered.
Pharmacokinetic	If the total radioactivity in	See above for collection stop criteria.	Changes made to urine/fecal collection

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Assessments, Urine sample collection, <b>Table 10</b>	<p>the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.</p>		stop criteria per site request to account for the amount of radioactivity likely to be recovered.
Pharmacokinetic Assessments, Fecal sample collection	<p>If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose</p>	<p><u>The discontinuation of fecal sample collections will be based on:</u></p> <ol style="list-style-type: none"> <li data-bbox="734 1057 1474 1176">1. <u>If the total radioactivity in the Day 14 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity &lt;85% (feces and urine), then fecal samples will be collected every 24 hours through Day 21.</u></li> <li data-bbox="734 1176 1474 1295">2. <u>If the total radioactivity in the Day 21 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity &lt;85% (feces and urine), then fecal samples will continue to be collected every 24 hours.</u></li> <li data-bbox="734 1295 1474 1414">3. <u>Feces sample collection will stop at the end of day Day 21 if the recovered radioactivity is &lt; 1% (per 24 hours) for the two consecutive days prior to Day 21 (Days 19 and 20). If this is not the case, then collection will stop as soon as the recovered</u></li> </ol>	Changes made to urine/fecal collection stop criteria per site request to account for the amount of radioactivity likely to be recovered.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
	given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.	radioactivity is <u>&lt; 1%</u> (per 24 hours) for two consecutive days after Day 21.	
Pharmacokinetic Assessments, Fecal sample collection, <a href="#">Table 11</a>	If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.	<u>See above for collection stop criteria</u>	Changes made to urine/fecal collection stop criteria per site request to account for the amount of radioactivity likely to be recovered.

Niraparib  
Protocol PR-30-5015-C Amendment 3 Summary of Changes

TESARO, Inc.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
Synopsis, Criteria for Evaluation, Pharmacokinetics; Pharmacokinetic Assessments, Sample analysis	<del>Extension study: Plasma niraparib concentrations will be used to determine the following PK parameters: <math>C_{max}</math>, <math>T_{max}</math>, <math>AUC_{0\text{-last}}</math>, <math>AUC_{0\text{-inf}}</math>, and <math>t_{1/2}</math>.</del>	N/A (deleted)	Modification made to account for note to file dated 01 June 2015
Assessments of Safety, Safety parameters, clinical laboratory assessments	N/A	<u>For any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization (WHO) criteria{REF}) and other sample testing reports related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the patient's study file.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
Assessments of Safety, Safety Parameters, (new sections)	N/A	<u>Blood and Tissue Samples</u> <u>Whole blood samples will be collected for all patients during screening and at EOT. Some samples will be used to determine eligibility per MDS/AML-related criteria (see Section 4). These test results must be received prior to randomization. For all eligible patients, remaining samples will be stored. Stored samples will be evaluated for mutations of selected myeloid-associated genes if the Sponsor's Medical Monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the patient develops MDS/AML). Details on blood and tissue sample collection can be found in the Laboratory Manual.</u> <u>New Malignancies</u> <u>Although overall survival is not an endpoint in this study, to monitor for MDS/AML and the occurrence of new malignancies, new malignancy information will be collected for all subjects via telephone every 90 days following the treatment discontinuation visit (subjects in the extension</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		<u>study only).</u>	
Adverse and Serious Adverse Events, Definition of Adverse Events	N/A (new section)	The event of disease progression is an efficacy criterion and is therefore <u>not considered an AE. If AEs/SAEs occur in relation to disease progression, then the AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 8.6.</u>	This change incorporates into the protocol an administrative letter that was issued on 06 Mar 2015 clarifying that disease progression alone is not considered an adverse event and that events occurring in relation to progression that meet the adverse event reporting criteria should be reported as noted in the relevant sections of the study protocol.
Adverse and Serious Adverse Events, Definition of Serious Adverse Events	Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE;	Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, <u>disease progression</u> , etc.) will not be considered an SAE	This change incorporates into the protocol an administrative letter that was issued on 06 Mar 2015 clarifying that disease progression alone is not considered an adverse event and that events occurring in relation to progression that meet the adverse event reporting criteria should be reported as noted in the relevant sections of the study protocol.
Adverse Events and Serious Adverse Events, Recording of Adverse Events	AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New AEs and SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see <a href="#">Table 1</a> , <a href="#">Table 2</a> , and <a href="#">Table 3</a> for schedules of events).	AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New <u>AEs and SAEs</u> (including deaths) will be collected for 30 days after treatment discontinuation (see Table 1, Table 2, and Table 3 for schedules of events) <u>or until new anticancer therapy is initiated.</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.
N/A (new section)	N/A (new section)	<u>Post-treatment Analyses</u> <u>Descriptive summary statistics will be used to summarize post study treatment data (ie, any new malignancy). In addition, the relationship between cytogenetic abnormalities and safety parameters may be</u>	This change was made to provide guidance on monitoring and following patients due to potential risk for MDS/AML observed in patients receiving a PARP inhibitor.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale																																																							
		<u>explored.</u>																																																								
Synopsis, Criteria for Evaluation, Pharmacokinetics; Statistics, Pharmacokinetic Analysis, Extension Study	<del>Extension Study Plasma concentrations of niraparib based on MS ion intensity and the derived PK parameters will be summarized using descriptive statistics and graphics.</del>	N/A (deleted)	Modification made to account for note to file dated 01 June 2015																																																							
<b>Table 12</b>	<b>PREVIOUS:</b> <b>Drugs Associated with QT Prolongation</b> <b>Table 1: Drugs Associated with QT prolongation</b>	<table border="1"> <thead> <tr> <th>Antiarrhythmics</th><th>Antimicrobials</th><th>Antidepressants</th><th>Antipsychotics</th><th>Others (including Selected Antiemetics)</th></tr> </thead> <tbody> <tr><td>Amiodarone</td><td>Levofloxacin</td><td>Amitriptyline</td><td>Haloperidol</td><td>Cisapride</td></tr> <tr><td>Sotalol</td><td>Ciprofloxacin</td><td>Desipramine</td><td>Droperidol</td><td>Sumatriptan</td></tr> <tr><td>Quinidine</td><td>Gatifloxacin</td><td>Imipramine</td><td>Quetiapine</td><td>Zolmitriptan</td></tr> <tr><td>Procainamide</td><td>Moxifloxacin</td><td>Doxepin</td><td>Thioridazine</td><td>Arsenic</td></tr> <tr><td>Dofetilide</td><td>Clarithromycin</td><td>Fluoxetine</td><td>Ziprasidone</td><td>Dolasetron</td></tr> <tr><td>Ibutilide</td><td>Erythromycin</td><td>Sertraline</td><td></td><td>Methadone</td></tr> <tr><td></td><td>Itraconazole</td><td>Venlafaxine</td><td></td><td>Metoclopramide</td></tr> <tr><td></td><td>Azithromycin</td><td></td><td></td><td>Domperidone</td></tr> <tr><td></td><td></td><td></td><td></td><td>Ondansetron</td></tr> <tr><td></td><td></td><td></td><td></td><td>Diphenhydramine</td></tr> </tbody> </table>	Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)	Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride	Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan	Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan	Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic	Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron	Ibutilide	Erythromycin	Sertraline		Methadone		Itraconazole	Venlafaxine		Metoclopramide		Azithromycin			Domperidone					Ondansetron					Diphenhydramine	This table was updated to refine list based on potential to cause QT prolongation, Torsades de Pointes, or drug-drug interaction; references were reformatted for consistency with other reference presentation in the document.
Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)																																																						
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride																																																						
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Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan																																																						
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic																																																						
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron																																																						
Ibutilide	Erythromycin	Sertraline		Methadone																																																						
	Itraconazole	Venlafaxine		Metoclopramide																																																						
	Azithromycin			Domperidone																																																						
				Ondansetron																																																						
				Diphenhydramine																																																						
<b>REVISED:</b> <b>Drugs Associated with Torsades de Pointes (TdP)</b> <b>Table 2: Drugs Associated with QT prolongation and TdP</b>																																																										

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )		Revised and/or Updated text (added text shown by <u>underline</u> )			Rationale
	<b>Antiarrhythmics</b>	<b>Antimicrobials</b>	<b>Antidepressants</b>	<b>Antipsychotics</b>	<b>Others (including Selected Antiemetics)</b>	
	Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride	
	Sotalol	Ciprofloxacin	Doxepin	Droperidol	Sumatriptan	
	Quinidine	Gatifloxacin		Quetiapine	Zolmitriptan	
	Procainamide	Moxifloxacin		Thioridazine	Arsenic	
	Dofetilide	Clarithromycin		Ziprasidone	Dolasetron	
	Ibutilide	Erythromycin			Methadone	
		Ketoconazole*				
		Itraconazole				

\*Topical use allowed for ketoconazole  
Cardiac Risk in the Young sponsored web site on Sudden Arrhythmic Death Syndrome.  
Available at:



## Summary of Protocol Changes

### Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

Previous Version: Version 2.1, dated 04 Dec 2014

Current Version: Version 3.0, dated 17 March 2015

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Global	N/A	Minor grammatical, typographical, and/or formatting/style errors and inconsistencies were corrected, including (but not limited to): replacing spelled numbers with numerals, adding articles before abbreviations, adding/removing hyphens, updating list of abbreviations, adjusting spacing after periods	Editorial changes were made throughout to improve clarity and flow, as well as maintain a consistent style.
Global	N/A	Various unsubstantial changes were made, ie, those which are unlikely to have a significant impact on the safety, physical, or mental integrity of the subjects; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of the investigational product.	Provide increased clarity to the study protocol. These changes will be documented in detail in the redline version of the final protocol.

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Exclusion Criteria #7	Subject received a transfusion (platelets or red blood cells) within 4 weeks of study drug administration.	Subject received ( <u>or is anticipated to receive</u> ) a platelet transfusion within 4 weeks of study drug administration.	Modified per site request: It is expected that several of the potential subjects will have had a transfusion to get the hematological values within the protocol criteria. Transfusions do not interfere with the Mass-Balance, thus site suggests to delete the criteria.
Summary 7.1 Overall Study Design	N/A	<u>Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria.</u>	Modified per site request: It is possible that some subjects could become non-evaluable (eg, missed PK), but would benefit from continued treatment (and would still meet inclusion/exclusion criteria).
Summary SOA (Table 3) 7.1 Overall Study Design	Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening. <u>The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2..... If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration..</u>	Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening ( <u>with the exception of complete blood count and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose</u> ).	Modified for clarification

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
7.4 Dose Adjustment Criteria	Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg ( $2 \times 100$ mg capsules) QD and subsequently to 100 mg ( $1 \times 100$ mg capsule) QD will be allowed based on treatment side effects.	<u>Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject. Treatment must be interrupted for any nonhematologic National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.02; HHS 2009) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days of dose interruption, at the Investigator's discretion, the subject may restart treatment with niraparib, but with a dose level reduction according to Table 5 if prophylaxis is not considered feasible, providing the subject has not already undergone the maximum number of 2 dose reductions allowed (to a minimum dose of 100 mg QD). Upon re-challenge, if the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted.</u>	Modified to harmonize with other protocols.
Summary SOA (Table 3)	Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg ( $2 \times 100$ mg capsules) QD and subsequently to 100 mg ( $1 \times 100$ mg capsule) QD will be allowed based on treatment side effects.	<u>Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject.</u>	Modified to harmonize with other protocols.
SOA (Table 1) SOA (Table 2) 7.1 Overall Study Design	Subjects have the option of staying overnight at the study center on Day -1.	<u>Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period.</u>	Added footnote to Clinical Laboratory Assessments, D-1 for clarification.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
SOA (Table 2) 11.1 Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling	N/A	<u>Participation in Part 2 of the study may extend beyond Day 22 if the amount of radioactivity found in the Day 22 urine or fecal samples is higher than 0.1% of the dose given. PK samples should continue to be collected every 7 days; the final PK draw should occur within ± 24 hours of the final urine or fecal sample (when both urine and fecal radioactivity is &lt;0.1% of the dose given).</u>	Addition to provide further instructions and clarity.
SOA (Table 3) 7.1 Overall Study Design	N/A	<u>Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. I</u>	Modified per site request: It is possible that some subjects could become non-evaluable (eg, missed PK), but would benefit from continued treatment (and would still meet inclusion/exclusion criteria).
SOA (Table 3)	Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.	Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. <u>For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.</u>	Modified for clarification.

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
SOA (Table 3)	<p>Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. No fasting period is required during the extension study. <del>Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100 mg capsules) QD and subsequently to 100 mg (1 × 100 mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments.</del> No new capsules will be dispensed at EOT.</p>	<p>Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. No fasting period is required during the extension study. No new capsules will be dispensed at EOT.</p>	<p>Dose interruption information moved for clarity and consistency</p>
7.4 Dose Adjustment Criteria	N/A	<p><u>Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient</u></p>	<p>Modified to harmonize with other protocols.</p>
Table 5, Footnote a	<p><del>Dose reductions for any NCI CTAE Grade 2 events that are bothersome to the subject will be permitted per the Investigator's judgment.</del></p>	<p><u>Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject.</u></p>	<p>Modified to harmonize with other protocols.</p>

Section(s)	Previous Text (deleted text shown by <del>strike-through</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
SOA (Table 1) SOA (Table 2)	All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.	Subjects have the option of reporting to <u>and/or staying</u> overnight at the study center on Day -1 <u>for the fasting period</u> . Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration.	Edited for clarity
SOA (Table 1) SOA (Table 2)	N/A	If subject comes to the center and/or chooses to be admitted on Day -1.	Footnote added to clarify instructions
SOA (Table 1) SOA (Table 2)	N/A	Must occur within 72 hours prior to dosing.	Footnote added to clarify instructions
SOA (Table 1)	Blood samples for PK analysis will be collected at the following times: predose (0 hour within 30 min prior to dose), Day 1 (1 [ $\pm 2$ min], 1.5 [ $\pm 2$ min], 2 [ <u>prior to IV infusion</u> ], 2.125 [ $\pm 1$ min], 2.25 ( <u>immediately after infusion</u> ),	Blood samples for PK analysis will be collected at the following times: predose (0 hour within 30 min prior to dose), Day 1 (1 [ $\pm 2$ min], 1.5 [ $\pm 2$ min], 2 [ <u>within 1 min prior to IV infusion</u> ], 2.125 [ $\pm 1$ min], 2.25 [ <u>within 1 min post-infusion</u> ]),	Dosing windows edited for clarity per PK
SOA (Table 3)	The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. <u>If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.</u>	The CBC includes hemoglobin, platelets, white blood cells, and neutrophils. <u>For Screening, blood samples should be drawn within 72 hours prior to study drug administration. Subsequent blood samples should be drawn prior to study drug administration.</u>	Modified to provide clarity.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
SOA (Table 3) 10.4 Study Drug Administration	N/A	<u>Niraparib is self-administered daily, except on study visit days. On days of study visits (eg, Cycle 1, Day 1, 8, 15, and 22; Cycle n, Day 1) subjects should refrain from taking niraparib until after clinical assessments are performed.</u>	Footnote added to provide clarity to dosing instructions.
8.3 Restrictions During Study	N/A	<u>Blood transfusions within the first 3 days post study drug administration are permissible if the blood transfusion is &lt; 500 mL/day.</u>	Added per site request. It is expected that several of the potential subjects will undergo a transfusion to get the hematological values within the protocol criteria.
7.4 Dose Adjustment Criteria	If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days, <del>the subject may restart treatment with niraparib, but with a dose level reduction according to Table 5 if prophylaxis is not considered feasible.</del> If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made.	If toxicity is appropriately resolved to baseline or CTCAE Grade 1 or less within 28 days <u>of dose interruption, at the Investigator's discretion the subject may restart treatment with niraparib, but with a dose level reduction according to Table 5 if prophylaxis is not considered feasible.</u> Upon re-challenge, if the event recurs at a similar or worse grade, then treatment should be interrupted again and, upon resolution, a further dose reduction must be made.	Modified to harmonize with other protocols.
9.2 Prior and Concomitant Medications	N/A	<u>Permitted anti-nausea medications are dexamethasone, aprepitant, and granisetron</u>	Clarification made per site request.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale																																				
11.0 Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling, Table 8	<table border="1" data-bbox="487 372 941 904"> <tr> <td>2 hr [prior to IV infusion]</td> <td>0 (predose)</td> </tr> <tr> <td>2.125 hr [<math>\pm 1</math> min]</td> <td>0.125</td> </tr> <tr> <td>2.25 hr [<u>immediately after</u>]</td> <td>0.25</td> </tr> <tr> <td>2.33 hr [<math>\pm 1</math> min]</td> <td>0.33</td> </tr> <tr> <td>2.66 hr [<math>\pm 1</math> min]</td> <td>0.66</td> </tr> <tr> <td>3 hr [<math>\pm 2</math> min]</td> <td>1</td> </tr> <tr> <td>4 hr [<math>\pm 5</math> min]</td> <td>2</td> </tr> <tr> <td>6 hr [<math>\pm 5</math> min]</td> <td>4</td> </tr> <tr> <td>12 hr [<math>\pm 15</math> min]</td> <td>10 [<math>\pm 1</math>]</td> </tr> </table>	2 hr [prior to IV infusion]	0 (predose)	2.125 hr [ $\pm 1$ min]	0.125	2.25 hr [ <u>immediately after</u> ]	0.25	2.33 hr [ $\pm 1$ min]	0.33	2.66 hr [ $\pm 1$ min]	0.66	3 hr [ $\pm 2$ min]	1	4 hr [ $\pm 5$ min]	2	6 hr [ $\pm 5$ min]	4	12 hr [ $\pm 15$ min]	10 [ $\pm 1$ ]	<table border="1" data-bbox="941 251 1554 796"> <tr> <td>2 hr [<u>within 1 min</u> prior to IV infusion]</td> <td>0<sup>c</sup></td> </tr> <tr> <td>2.125 hr [<math>\pm 1</math> min]<sup>d</sup></td> <td>0.125<sup>c</sup></td> </tr> <tr> <td>2.25 hr [<u>within 1 min post-infusion</u>]<sup>e</sup></td> <td>0.25<sup>c</sup></td> </tr> <tr> <td>2.33 hr [<math>\pm 1</math> min]<sup>f</sup></td> <td>0.33<sup>c</sup></td> </tr> <tr> <td>2.66 hr [<math>\pm 1</math> min]<sup>g</sup></td> <td>0.66<sup>c</sup></td> </tr> <tr> <td>3 hr [<math>\pm 2</math> min]</td> <td>1<sup>c</sup></td> </tr> <tr> <td>4 hr [<math>\pm 5</math> min]</td> <td>2<sup>c</sup></td> </tr> <tr> <td>6 hr [<math>\pm 5</math> min]</td> <td>4<sup>c</sup></td> </tr> <tr> <td>12 hr [<math>\pm 15</math> min]</td> <td>10<sup>c</sup></td> </tr> </table> <p><sup>c</sup> Refer to Time From Oral Dose column for collection windows for the 0-10 hr Time From Start of IV Infusion.</p> <p><sup>d</sup> 2 hr 7.5 min</p> <p><sup>e</sup> 2 hr 15 min</p> <p><sup>f</sup> 2 hr 20 min</p> <p><sup>g</sup> 2 hr 40 min</p>	2 hr [ <u>within 1 min</u> prior to IV infusion]	0 <sup>c</sup>	2.125 hr [ $\pm 1$ min] <sup>d</sup>	0.125 <sup>c</sup>	2.25 hr [ <u>within 1 min post-infusion</u> ] <sup>e</sup>	0.25 <sup>c</sup>	2.33 hr [ $\pm 1$ min] <sup>f</sup>	0.33 <sup>c</sup>	2.66 hr [ $\pm 1$ min] <sup>g</sup>	0.66 <sup>c</sup>	3 hr [ $\pm 2$ min]	1 <sup>c</sup>	4 hr [ $\pm 5$ min]	2 <sup>c</sup>	6 hr [ $\pm 5$ min]	4 <sup>c</sup>	12 hr [ $\pm 15$ min]	10 <sup>c</sup>	Modifications made for clarity and consistency.
2 hr [prior to IV infusion]	0 (predose)																																						
2.125 hr [ $\pm 1$ min]	0.125																																						
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Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
12.1.2 Medical History and Cancer History	<p>The following will be documented for cancer history:</p> <ul style="list-style-type: none"><li>• Date of first diagnosis</li><li>• Tumor type</li><li>• Stage at time of initial diagnosis</li><li>• Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed</li><li>• Date of start of first treatment</li><li>• Agents used in first treatment</li><li>• Date of last dose of first treatment</li><li>• Dates of start of all subsequent treatments</li><li>• Agents used in all subsequent treatments</li><li>• Dates of last dose of all subsequent treatments</li><li>• Date of recurrence for each treatment</li></ul>	<p>The following will be documented for cancer history:</p> <ul style="list-style-type: none"><li>• Date of first diagnosis</li><li>• Tumor type</li><li>• Stage at time of initial diagnosis</li><li>• Tumor grade</li><li>• Date of start of first treatment</li><li>• Agents used in first treatment</li><li>• Date of last dose of first treatment</li><li>• Date of relapse for each treatment</li></ul>	Modified to harmonize with SAP and eCRFs.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
12.1.9.2 Pregnancy Screen	A urine pregnancy test will be performed during the Screening Visit for the extension study and every 3 months thereafter (Cycle 4, Cycle 7, etc.).	A urine pregnancy test will be performed every 3 months <u>for the duration of the study (ie, Cycle 4, Cycle 7, etc.)</u> .	Clarified to be in agreement with SOE
13.3.3 Vital Signs	Flags will be attached to values outside of the reference limits along with the PI's assessment of clinical significance. Clinically significant vital signs will be summarized separately by group and study visit, and individual data listings of clinically significant vital signs will also be presented for each subject	N/A	Modified per SAP
12.3.4 Electrocardiograms	Clinically significant ECG parameters will be summarized separately by group	N/A	Modified per SAP
13.3.5 Clinical Laboratory Assessments	Shift tables will also be presented for select chemistry and hematology laboratory parameters.	Shift tables <u>based on normal ranges</u> will also be presented for select chemistry and hematology laboratory parameters.	Modified per SAP
12.1.8.1 Parts 1 and 2 Laboratory Assessments	N/A	If the Screening Visit laboratory assessments occur within 72 hours prior to dosing, then the assessments do not need to be repeated at Day -1.	Modified to provide clarity.
12.1.8.2 Extension Study Laboratory Assessments	N/A	<u>Blood samples should be drawn prior to study drug administration (within 72 hours prior to dosing).</u>	Modified to provide clarity.



## Summary of Protocol Changes

### Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

Previous Version: Version 1.0, dated 28 May 2014

Current Version: Amendment 1, Version 2.1, dated 04 December 2014

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
Global	N/A	Minor grammatical, typographical, and/or formatting/style errors and inconsistencies were corrected, including (but not limited to): replacing spelled numbers with numerals, adding articles before abbreviations, adding/removing hyphens, updating list of abbreviations, adjusting spacing after periods	Editorial changes were made throughout to improve clarity and flow, as well as maintain a consistent style.
Global	N/A	Various unsubstantial changes were made, ie, those which are unlikely to have a significant impact on the safety, physical, or mental integrity of the subjects; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of the investigational product.	Provide increased clarity to the study protocol. These changes will be documented in detail in the redline version of the final protocol.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
Global	N/A	Two spaces after periods were replaced with one space.	Spacing change was made to maintain a consistent style across sponsor programs.
- List of abbreviations - Global - Tables/Figures	N/A	In the list of abbreviations, rows were deleted and added. In the body text, abbreviation definitions and usage were revised as needed. In Tables/Figures, lists of abbreviations were added as needed.	Abbreviations were changed to provide additional definitions and improve clarity.
Global	TESARO	<u>The Sponsor</u>	“TESARO” was replaced with “the Sponsor” so that Tesaro is referred to in the same way throughout the document.
Global	Treatment discontinuation	<u>End of Treatment (EOT)</u>	“treatment discontinuation” was replaced with “end of treatment” (or EOT) for consistency with other Tesaro protocols.
- Title page - Document headers and footers	N/A	Amendment number and date were updated. Headers and footers were updated.	Changed to reflect Amendment 1 information. Headers and footers updated per new Regulatory style.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)	Rationale
- Sponsor signature page	PI <del>Canadian PhD</del> Chief Medical Officer	PI <u>MD</u> <u>Senior Medical Director</u>	The responsible medical expert for the sponsor was updated to reflect a personnel change made by the sponsor.
- Synopsis, Name of Active Ingredient	(3S)-3-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl) piperidine (tosylate monohydrate salt)	<u>Niraparib</u>	Changed to the international nonproprietary name for consistency with other protocols.
- Synopsis, Study Period (years)	Estimated first subject enrolled: <del>December 2014</del>	<u>February 2015</u>	Date changed to reflect current enrollment expectations.
- Synopsis, Methodology, Part 1 - Synopsis, Methodology, Part 2 <u>- 7.1 Overall Study Design, Part 1</u> <u>- 7.1 Overall Study Design, Part 2</u>	After <del>the</del> Screening Visit ( <del>occurring</del> within the 3 weeks prior to study drug administration), subjects <del>will be admitted to the study center the afternoon prior to study drug administration (ie, Study Day 1, at least 12 hours prior to study drug administration).</del>	The Screening Visit <u>will occur</u> within the 3 weeks prior to study drug administration. <u>All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events.</u> <u>Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.</u>	To allow for operational flexibility, Day -1 criteria modified to account for optional overnight stay.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<ul style="list-style-type: none"> <li>- 7.1 Overall Study Design, Part 1</li> <li>- 7.1 Overall Study Design, Part 2</li> </ul>	N/A	<p><u>Water is permissible during the overnight fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration.</u></p>	Addition made to account for operational flexibility given the long fasting period required of subjects.
<ul style="list-style-type: none"> <li>- Synopsis, Methodology, Extension study</li> <li>- 7.1 Overall Study Design, Extension study</li> </ul>	<p>On the same day that subjects complete Part 1 or 2 of the study, subjects <u>will</u> be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments.</p>	<p>On the same day that subjects complete Part 1 or 2 of the study, subjects <u>may</u> be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments.</p>	Changed to clarify that enrollment in the extension study is contingent upon meeting inclusion/exclusion criteria.
<ul style="list-style-type: none"> <li>- Synopsis, Methodology, Extension study</li> <li>- 7.1 Overall Study Design, Extension study</li> </ul>	<p>Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria (<a href="#">Section</a>).</p>	<p>Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria (<a href="#">Section 8.4</a>), <u>or until the subject can be transitioned to the roll-over study (if eligible, see below).</u></p>	Changes made to clarify the difference between the main study vs. extension study vs. roll-over study.
<ul style="list-style-type: none"> <li>- Synopsis, Methodology, Roll-over study</li> <li>- 7.1 Overall Study Design, Roll-over study</li> </ul>	N/A	<p><b><u>Roll-over study (all eligible subjects):</u></b> Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study <u>when the protocol becomes available.</u></p>	Additions made to clarify the difference between the main study vs. extension study vs. roll-over study.
<ul style="list-style-type: none"> <li>- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Inclusion #6</li> </ul>	N/A	<p><u>Female subjects of childbearing potential must have a negative serum pregnancy test (beta hCG) within 72 hours prior to receiving the first dose of study drug.</u></p>	Addition made to clarify the need for a negative serum pregnancy test prior to enrollment.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Inclusion #7	Male and female subjects of <u>childbearing</u> potential must use adequate birth control for the duration of study participation ( <a href="#">Section 8.3</a> ).	Male and female subjects of <u>reproductive</u> potential must use adequate birth control for the duration of study participation ( <a href="#">Section 8.3</a> ).	Re-worded to account for need for male birth control
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #1	Subject has undergone palliative radiotherapy within 1 week of <u>the Screening Visit</u> , encompassing >20% of the bone marrow.	Subject has undergone palliative radiotherapy within 1 week of <u>study drug administration</u> , encompassing >20% of the bone marrow.	Radiotherapy may not have occurred within one week of study drug administration, not within one week of the screening visit.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #5	Subject has had major surgery within 3 weeks of <u>the Screening Visit</u> or has not recovered from all effects of any major surgery.	Subject has had major surgery within 3 weeks of <u>study drug administration</u> or has not recovered from all effects of any major surgery.	Major surgery may not have occurred within three weeks of study drug administration, not within three weeks of the screening visit.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #7	N/A	<u>Subject received a transfusion (platelets or red blood cells) within 4 weeks of study drug administration.</u>	Additional exclusion criterion for consistency with other niraparib studies.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #14	Subject is starting chemotherapy <u>within 3 weeks of the Screening Visit</u> .	Subject is starting chemotherapy within 3 weeks of <u>study drug administration</u> .	Chemotherapy may not have occurred within three weeks of study drug administration, not within three weeks of the screening visit.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion # 16	Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours of study drug administration.	Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, <u>and/or within 6 hours after study drug administration.</u>	Detail added to clarify use of the indicated medications following study drug administration
General	N/A	<u>IB version 3.0, 09 April 2014</u>	Added IB version number and date for precision and clarity.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion # 17	Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to the <u>Screening Visit</u> ) or dependence or is unable to abstain from alcohol for the duration of the study.	Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to <u>study drug administration</u> ) or dependence or is unable to abstain from alcohol for the duration of the study.	Chronic alcohol use may not have occurred within 30 days prior to study drug administration, not within 30 days prior to the screening visit.
- Overall Study Design, <a href="#">Table 2</a> , <a href="#">Table 3</a> , <a href="#">Table 4</a>	N/A	Moved to immediately after Synopsis ( <a href="#">Section 2</a> ). Now numbered Table 1, 2, and 3.	Ethics Committee request
- Overall Study Design, Table 2 (revised as 1)	<i>See below for original table</i>	<i>See below for revised table</i>	Updated per discussions: - Serum pregnancy test at screening and at EOT. - ECOG performance test at screening and EOT - PK blood sample

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
			windows updated - Oral temperature changed to aural/tympanic - Footnotes updated as described herein.

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)											Rationale
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**(ORIGINAL) Table 2: Schedule of Assessments: Part 1**

Assessment or Procedure	-21 to -2 Screening Visit	Day Relative to First Dose of Study Drug											
		-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 <b>End of Part 1</b>
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X	X											X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>c</sup>	X												
Clinical laboratory assessments <sup>d</sup>	X	X				X							X
Serum pregnancy test	X												
Electrocardiogram (12-lead) <sup>e</sup>	X		X										X
ECOG performance status	X												
Confirm diagnosis with CT scan <sup>f</sup>	X												
Screening number assignment	X												
Subject confinement		X	X	X	X	X							

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )	Revised and/or Updated text (added text shown by <u>underline</u> )										Rationale
Subject dosing number assignment			<del>X</del>									
Niraparib oral administration <sup>g</sup>			X									
[ <sup>14</sup> C]-niraparib IV infusion <sup>h</sup>			X									
Pharmacokinetic blood sampling <sup>i</sup>			X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous.

<sup>a</sup> Subjects will be admitted to the study center the afternoon prior to study drug administration (at least 12 hours prior to study drug administration).

<sup>b</sup> Vital signs include blood pressure, pulse rate, and oral temperature. Vital signs will be collected prior to study drug administration on Day 1 and prior to any blood draws on other study days.

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>d</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. On Day 1, blood samples should be drawn prior to study drug administration.

<sup>e</sup> Subjects will have a 12-lead electrocardiogram at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>f</sup> Subjects must provide a CT scan to confirm their diagnosis. A CT scan is performed every 8 weeks as part of standard of care.

<sup>g</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>h</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>i</sup> Blood samples for pharmacokinetic analysis will be collected at the following times: predose (0 hour), Day 1 (1, 1.5, 2 [prior to IV infusion], 2.125, 2.25, 2.33, 2.66, 3, 4, 6, and 12 [ $\pm$ 4] hours postdose), Day 2 (24 [ $\pm$ 1] hours postdose), Day 3 (48 [ $\pm$ 2] hours postdose), Day 4 (72 [ $\pm$ 4] hours postdose), Day 5 (96 [ $\pm$ 4] hours postdose), Day 7 (144 [ $\pm$ 4] hours postdose), Day 9 (192 [ $\pm$ 8] hours postdose), Day 11 (240 [ $\pm$ 12] hours postdose), Day 13 (288 [ $\pm$ 12] hours postdose), Day 15 (336 [ $\pm$ 12] hours postdose), and Day 22 (504 [ $\pm$ 12] hours postdose).

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )											Rationale
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**(REVISED) Table 1: Schedule of Assessments: Part 1**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X	X											X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>c</sup>	X												
Clinical laboratory assessments <sup>d</sup>	X	X											X
Serum pregnancy test ( <u>women of childbearing potential</u> )	X												X <sup>e</sup>
Electrocardiogram (12-lead) <sup>f</sup>	X		X										X
ECOG performance status	X												X <sup>e</sup>
Confirm diagnosis with CT scan <sup>g</sup>	X												

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )										Rationale
Subject confinement		<del>X<sup>h</sup></del>	X	X	X	X						
Niraparib oral administration <sup>i</sup>			X									
[ <sup>14</sup> C]-niraparib IV infusion <sup>j</sup>			X									
Pharmacokinetic blood sampling <sup>k</sup>			X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X <sup>e</sup>
Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous												

<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>d</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>e</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see Section 12.4).

<sup>f</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>g</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>h</sup> If subject chooses to be admitted on Day -1.

<sup>i</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>j</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [prior to IV infusion], 2.125 [ $\pm 1$  min], 2.25 (immediately after infusion), 2.33 [ $\pm 1$  min], 2.66 [ $\pm 1$  min], 3 [ $\pm 2$  min], 4 [ $\pm 5$  min], 6 [ $\pm 5$  min], and 12 hours [ $\pm 15$  min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<sup>1</sup> Serious adverse events (SAEs) will be recorded up to 30 days after EOT.			
- Overall Study Design, <a href="#">Table 2</a>	<i>See below for original table</i>	<i>See below for revised table</i>	<p>Updated as per discussion:</p> <ul style="list-style-type: none"> <li>- Subject confinement not necessary on day -1</li> <li>- Serum pregnancy test at screening and at EOT.</li> <li>- ECOG performance test at screening and EOT</li> <li>- PK and metabolite blood sample windows updated</li> <li>- Oral temperature changed to aural/tympanic</li> <li>- Footnotes updated as described herein.</li> </ul>

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
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**(ORIGINAL) Table 3: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																		<b>22<sup>b</sup></b> End of Part 2
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Informed consent	X																		
Subject demographics and baseline characteristics	X																		
Medical history and cancer history	X																		
Inclusion/exclusion criteria	X																		
Physical examination	X																	X	
Height (cm)	X																		
Weight (kg)	X	X																X	
Body mass index (kg/m <sup>2</sup> )	X																		
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
HBV/HCV/HIV screening <sup>d</sup>	X																		
Clinical laboratory assessments <sup>e</sup>	X	X															X	X	
Serum pregnancy test	X																		
Electrocardiogram (12-lead) <sup>f</sup>	X		X															X	
ECOG performance status	X																		
Confirm diagnosis with CT scan <sup>g</sup>	X																		

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )												Revised and/or Updated text (added text shown by <u>underline</u> )												Rationale	
Screening number assignment	<del>X</del>																									
Subject confinement	X X X X X X X X X X X X																									
Subject dosing number assignment	<del>X</del>																									
[ <sup>14</sup> C]-niraparib administration <sup>h</sup>	X																									
Pharmacokinetic blood sampling <sup>i</sup>	X X X X X X X X X X X X																							X X		
Blood sample for metabolite profiling <sup>j</sup>	X X X X X X X X X X X X																							X X		
Urine collection <sup>k</sup>	X X X X X X X X X X X X																							X X	X X	
Fecal collection <sup>l</sup>	X X X X X X X X X X X X																							X X	X X	
Prior/concomitant medication and AE monitoring	X X X X X X X X X X X X																							X X		

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> Subjects will be admitted to the study center the afternoon prior to study drug administration (at least 12 hours prior to study drug administration).

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote k and Footnote l), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and ~~oral~~ temperature. Vital signs will be collected prior to study drug administration on Day 1 and prior to any blood draws on other study days.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. On Day 1, blood samples should be drawn prior to study drug administration.

<sup>f</sup> Subjects will have a 12-lead electrocardiogram at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>g</sup> Subjects must provide a CT scan to confirm their diagnosis. ~~A CT scan is performed every 8 weeks as part of standard of care.~~

<sup>h</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100  $\mu$ Ci of radioactivity, after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<sup>i</sup>			
<sup>l</sup>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )		Revised and/or Updated text (added text shown by <u>underline</u> )															Rationale	
Assessment or Procedure	Day Relative to First Dose of Study Drug																		<b>22<sup>b</sup></b> End of Part 2
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Informed consent	X																		
Subject demographics and baseline characteristics	X																		
Medical history and cancer history	X																		
Inclusion/exclusion criteria	X																		
Physical examination	X																	X	
Height (cm)	X																		
Weight (kg)	X	X																X	
Body mass index (kg/m <sup>2</sup> )	X																		
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
HBV/HCV/HIV screening <sup>d</sup>	X																		
Clinical laboratory assessments <sup>e</sup>	X	X															X	X	
Serum pregnancy test ( <u>women of childbearing potential</u> )	X																	X <sup>f</sup>	
Electrocardiogram (12-lead) <sup>g</sup>	X		X															X	
ECOG performance status	X																	X <sup>f</sup>	
Confirm diagnosis with CT scan <sup>h</sup>	X																		
Subject confinement		X <sup>i</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X				

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )						Revised and/or Updated text (added text shown by <u>underline</u> )										Rationale		
[ <sup>14</sup> C]-niraparib administration <sup>j</sup>			X																
Pharmacokinetic blood sampling <sup>k</sup>			X	X	X	X	X	X											X X
Blood sample for metabolite profiling <sup>l</sup>			X	X	X	X	X	X											X X
Urine collection <sup>m</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X X	
Fecal collection <sup>n</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X X	
Prior/concomitant medication and AE monitoring <sup>o</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X <sup>f</sup>		
Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.																			

<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote m and Footnote n), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.

<sup>f</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see Section 12.4).

<sup>g</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>h</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.

<sup>i</sup> If subject chooses to be admitted on Day -1.

<sup>j</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity (3 x 100-mg capsules, labeled active pharmaceutical ingredient [3 x 33.3 µCi of radioactivity]), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 min prior to dose), Day 1 (1 [ $\pm 2$  min], 1.5 [ $\pm 2$  min], 2 [ $\pm 2$  min]),

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <b>strikethrough</b> )	<b>Revised and/or Updated text</b> (added text shown by <b>underline</b> )	<b>Rationale</b>
	<del>min], 3 [<math>\pm 2</math> min], 4 [<math>\pm 5</math> min], 6 [<math>\pm 5</math> min], and 12 hours [<math>\pm 15</math> min] postdose), Day 2 (24 [<math>\pm 1</math>] hours postdose), Day 3 (48 [<math>\pm 2</math>] hours postdose), Day 4 (72 [<math>\pm 4</math>] hours postdose), Day 5 (96 [<math>\pm 4</math>] hours postdose), Day 6 (120 [<math>\pm 4</math>] hours postdose), Day 8 (168 [<math>\pm 4</math>] hours postdose), Day 11 (240 [<math>\pm 12</math>] hours postdose), Day 15 (336 [<math>\pm 12</math>] hours postdose), and Day 22 (504 [<math>\pm 12</math>] hours postdose).</del>		
<sup>l</sup>	Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, <u>within 30 min prior to dose</u> ), Day 1 (1 [ $\pm 2$ min], 2 [ $\pm 2$ min], 3 [ $\pm 2$ min], 6 [ $\pm 5$ min], and 12 [ $\pm 15$ min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).		
<sup>k</sup>	Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.		
<sup>l</sup>	Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.		
<sup>o</sup>	<u>SAEs will be recorded up to 30 days after EOT.</u>		
- Overall Study Design, <a href="#">Table 3</a>	<i>See below for original table</i>	<i>See below for revised table</i>	Updated as per discussion: - Serum pregnancy test at screening and at EOT. - ECOG performance test at screening and EOT - PK blood sample windows updated - Oral temperature changed to

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
			aural/tympanic - Footnotes updated as described herein.

**(ORIGINAL) Table 4: Schedule of Assessments: Open-label Extension Study**

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )	Revised and/or Updated text (added text shown by <u>underline</u> )				Rationale	
Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b,c</sup>	Treatment Discontinuation <sup>d</sup>
		Day 1	Day 8	Day 15	Day 21	Day 1	
Inclusion/exclusion criteria <sup>e</sup>	X	✗					
Physical examination		✗		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>f</sup>	X	✗	X	X	X	X	X
Complete blood count <sup>g</sup>	X		✗	X	X	X	X
Coagulation and blood chemistry <sup>h</sup>	X			X		X	X
Pregnancy test <sup>i</sup>	X					X	X
Study drug dispensed/collected <sup>j</sup>			✗			X	X
Electrocardiogram (12-lead) <sup>k</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>l</sup>		X				X	X
Concomitant medication and AE monitoring <sup>m</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> On the same day that subjects complete Part 1 or 2 of the study, subjects will be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). ~~Subjects have 7 days to complete the screening assessments, and the Screening Visit (+7 days) and Cycle 1/Day 1 Visit can occur on the same day.~~

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days.

<sup>c</sup> Visits will continue approximately every 4 weeks until treatment discontinuation.

<sup>d</sup> The visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria.

<sup>e</sup> If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the inclusion/exclusion criteria should only be reviewed once.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<sup>f</sup>	Vital signs include blood pressure, pulse rate, and <del>oral</del> temperature. Vital signs will be collected prior to study drug administration and blood draws. If the Screening Visit ( <del>+7 days</del> ) and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.		
<sup>g</sup>	The <del>complete blood count</del> includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit ( <del>+7 days</del> ) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.		
<sup>h</sup>	Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit ( <del>+7 days</del> ) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.		
<sup>i</sup>	<del>A urine pregnancy test will be conducted at the Screening Visit and every 3 months thereafter. A serum pregnancy test will be conducted at treatment discontinuation.</del>		
<sup>j</sup>	Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. No new capsules will be dispensed at treatment discontinuation.		
<sup>k</sup>	Subjects will have a 12-lead electrocardiogram at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at <del>treatment discontinuation</del> .		
<sup>l</sup>	Blood samples for pharmacokinetic analysis will be collected at the following times: Cycle 1/Day 1 Visit (predose and 2 hours postdose), Cycle 2/Day 1 Visit (predose and 2 hours postdose), Cycle 4/Day 1 Visit (predose), and Cycle 8/Day 1 Visit (predose).		
<sup>m</sup>	Serious AEs will be recorded up to 30 days after treatment discontinuation.		
<b>(REVISED) Table 3: Schedule of Assessments: Open-label Extension Study</b>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )				Rationale	
Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c</sup>
		Day 1	Day 8	Day 15	Day 22	Day 1	
Inclusion/exclusion criteria	X						
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>d</sup>	X	X	X	X	X	X	X
Complete blood count (CBC) <sup>e</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>f</sup>	X			X		X	X
Pregnancy test (women of childbearing potential) <sup>g</sup>	X					X	X
Study drug dispensed/collected <sup>h</sup>		X				X	X
Electrocardiogram (12-lead) <sup>i</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>j</sup>		X				X	X
Concomitant medication and AE monitoring <sup>k</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> Upon completion of Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). [The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening. The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2.](#)

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days. [Visits \(except Cycle 1\) will continue approximately every 4 weeks until treatment discontinuation](#)

<sup>c</sup> The EOT visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria. If the subject discontinues due to disease progression, then the CT scan (taken per standard of care) closest to the time of progression

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		<u>(EOT) should be provided.</u>	
<sup>f</sup> Vital signs include blood pressure, pulse rate, and <u>aural (tympanic)</u> temperature. On Day 1, vital signs should be collected prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.			
<sup>e</sup> The <u>CBC</u> includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.			
<sup>f</sup> Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase ( <u>AST</u> ), alanine aminotransferase ( <u>ALT</u> ), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.			
<sup>g</sup> A serum pregnancy test will be conducted at the Screening Visit and at EOT. A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.).			
<sup>h</sup> Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. <u>No fasting period is required during the extension study.</u> Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. No new capsules will be dispensed at EOT.			
<sup>i</sup> Subjects will have a 12-lead ECG at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at <u>EOT</u> .			
<sup>j</sup> Blood samples for PK analysis will be collected at the following times: Cycle 1/Day 1 Visit ( <u>within 30 min predose and 2 hours ±15 min postdose</u> ), Cycle 2/Day 1 Visit ( <u>within 30 min predose and 2 hours ±15 min postdose</u> ), Cycle 4/Day 1 Visit ( <u>within 30 min predose</u> ), and Cycle 8/Day 1 Visit ( <u>within 30 min predose</u> ).			
<sup>k</sup> SAEs will be recorded up to 30 days after EOT.			
<p>- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion # 18</p>	<p>Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of the <u>Screening Visit</u>.</p>	<p>Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of <u>study drug administration</u>.</p>	<p>Participation in another clinical trial may not have occurred within 21 days of study drug administration, not within 21 days of the screening visit.</p>
<p>- Overall Study Design, Table 2, Table 3, Table 4 (revised to Tables 1, 2, and 3)</p> <p>- Overall Study Design, Parts 1, 2,</p>	<p>Vital signs include blood pressure, pulse rate, and <u>oral</u> temperature. <u>Vital signs will be collected prior to study</u></p>	<p>Vital signs include blood pressure, pulse rate, and <u>aural (tympanic)</u> temperature. <u>On Day 1, vital signs should be collected prior to study drug administration.</u></p>	<p>Not necessary to define when vital signs are to be collected in visits that occur after study</p>

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
and Extension Study - Safety Parameters, Vital Signs	<u>drug administration on Day 1 and prior to any blood draws on other study days.</u>		drug administration.
- Medical History and Cancer History	Subjects must provide a previous CT scan to confirm their cancer diagnosis. A CT scan is performed every 8 weeks as part of standard of care.	Subjects must provide <u>the most recent</u> CT scan ( <u>taken prior to enrollment</u> ) to confirm their cancer diagnosis. <u>CT scans should be performed per standard of care. If the subject discontinues due to disease progression, then the CT scan closest to the time of progression (EOT) should also be provided.</u>	Clarifications and revisions made per medical input.
- Overall Study Design, <b>Tables 2</b> and <b>3</b> (revised to Tables 1 and 2) - Overall Study Design, Parts 1 and 2 - Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling	Blood samples for pharmacokinetic analysis will be collected at the following times: predose (0 hour), Day 1 (1, 1.5, 2 [prior to IV infusion], 2.125, 2.25, 2.33, 2.66, 3, 4, 6, and 12 [ $\pm 1$ ] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).	Blood samples for PK analysis will be collected at the following times: predose (0 hour, <u>within 30 min prior to dose</u> ), Day 1 (1 [ $\pm 2$ min], 1.5 [ $\pm 2$ min], 2 [ $\pm 2$ min], 3 [ $\pm 2$ min], 4 [ $\pm 5$ min], 6 [ $\pm 5$ min], and 12 hours [ $\pm 15$ min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).	Sampling windows revised for consistency and precision

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<ul style="list-style-type: none"> <li>- Overall Study Design, <a href="#">Table 2</a> (revised to Table 1)</li> <li>- Overall Study Design, Part 1</li> <li>- Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling</li> </ul>	<p>Blood samples for metabolite profiling will be collected at the following times: predose (0 hour), Day 1 (1, 2, 3, 6, and 12 [<math>\pm 1</math>] hours postdose), Day 2 (24 [<math>\pm 1</math>] hours postdose), Day 3 (48 [<math>\pm 2</math>] hours postdose), Day 4 (72 [<math>\pm 4</math>] hours postdose), Day 5 (96 [<math>\pm 4</math>] hours postdose), Day 6 (120 [<math>\pm 4</math>] hours postdose), Day 8 (168 [<math>\pm 4</math>] hours postdose), Day 11 (240 [<math>\pm 12</math>] hours postdose), Day 15 (336 [<math>\pm 12</math>] hours postdose), and Day 22 (504 [<math>\pm 12</math>] hours postdose).</p>	<p>Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, <u>within 30 min prior to dose</u>), Day 1 (<u>1 [<math>\pm 2</math> min]</u>, <u>2 [<math>\pm 2</math> min]</u>, <u>3 [<math>\pm 2</math> min]</u>, <u>6 [<math>\pm 5</math> min]</u>, and <u>12 [<math>\pm 15</math> min]</u> hours postdose), Day 2 (24 [<math>\pm 1</math>] hours postdose), Day 3 (48 [<math>\pm 2</math>] hours postdose), Day 4 (72 [<math>\pm 4</math>] hours postdose), Day 5 (96 [<math>\pm 4</math>] hours postdose), Day 6 (120 [<math>\pm 4</math>] hours postdose), Day 8 (168 [<math>\pm 4</math>] hours postdose), Day 11 (240 [<math>\pm 12</math>] hours postdose), Day 15 (336 [<math>\pm 12</math>] hours postdose), and Day 22 (504 [<math>\pm 12</math>] hours postdose).</p>	<p>Sampling windows revised for consistency and precision</p>
<ul style="list-style-type: none"> <li>- Overall Study Design, <a href="#">Table 3</a> (revised to Table 2)</li> <li>- Overall Study Design, Part 2</li> <li>- Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling</li> </ul>	<p>Blood samples for pharmacokinetic analysis will be collected at the following times: Cycle 1/Day 1 Visit (predose and 2 hours postdose), Cycle 2/Day 1 Visit (predose and 2 hours postdose), Cycle 4/Day 1 Visit (predose), and Cycle 8/Day 1 Visit</p>	<p>Blood samples for PK analysis will be collected at the following times: Cycle 1/Day 1 Visit (<u>within 30 min</u> predose and 2 hours <u><math>\pm 15</math> min</u> postdose), Cycle 2/Day 1 Visit (<u>within 30 min</u> predose and 2 hours <u><math>\pm 15</math> min</u> postdose), Cycle 4/Day 1 Visit (<u>within 30 min</u> predose), and Cycle 8/Day 1 Visit (<u>within 30 min</u> predose).</p>	<p>Sampling windows revised for consistency and precision</p>

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
	(predose).		
- Overall Study Design, <a href="#">Table 4</a> . (revised to Table 3) - Overall Study Design, Extension Study	A <u>urine</u> pregnancy test will be conducted at the Screening Visit and <u>every 3 months thereafter</u> . <u>A serum pregnancy test will be conducted at treatment discontinuation</u> .	A <u>serum</u> pregnancy test will be conducted at the Screening Visit and <u>at EOT</u> . <u>A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.)</u> .	Corrected timing of serum vs. urine pregnancy tests, and clarified frequency of the tests.
- Overall Study Design, <a href="#">Table 2</a> , <a href="#">Table 3</a> (revised to Tables 1 and 2) - Overall Study Design, Parts 1 and 2	N/A	<u>All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG prior to study exit. Discontinued subjects will be followed for safety per section 12.4.</u>	Revised to include additional study exit criteria for any patients who do not enroll in the extension study.
- Overall Study Design, Table 4 (revised to Table 3) - Overall Study Design, Extension Study	Subjects have <u>7 days to complete the screening assessments, and the Screening Visit (+7 days) and Cycle 1/Day 1 Visit can occur on the same day</u> .	<u>The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening. The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2.</u>	Clarified
- Overall Study Design, Table 4 (revised to Table 3) - Overall Study Design, Extension Study	If the Screening Visit ( <u>+7 days</u> ) and Cycle 1/Day 1 Visit occur on the same day, the inclusion/exclusion criteria should only be reviewed once.	If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.	Clarified
- Overall Study Design, Table 4 (revised to Table 3)	The <u>complete blood count</u> includes hemoglobin,	The <u>CBC</u> includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should	Clarified

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<p>- Overall Study Design, Extension Study</p>	<p>platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.</p>	<p>be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.</p>	
<p>- Overall Study Design, <b>Table 4</b> (revised to Table 3)</p> <p>- Overall Study Design, Extension Study</p>	<p>Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (<u>AST</u>), alanine aminotransferase (<u>ALT</u>), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug</p>	<p>Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase (<u>AST</u>), alanine aminotransferase (<u>ALT</u>), blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration</p>	<p>Clarified</p>

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
	administration. If the Screening Visit ( <del>+7 days</del> ) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.		
- Introduction, Risks and Benefits	N/A	<u>The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs.</u>	
- Dose Adjustment Criteria, Table 6	N/A	<u>*For patients with platelet count <math>\leq</math> 10,000/<math>\mu</math>L prophylactic platelet transfusion per guidelines may be considered (Schiffer et al., 2001; Slichter, 2007). For patients taking anticoagulation or antiplatelet drugs consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as <math>\leq</math> 20,000/<math>\mu</math>L.</u>	
- Dose Adjustment Criteria, Table 6	Platelet count 75,000-100,000/ $\mu$ L Second occurrence of platelet count 75,000-100,000/ $\mu$ L	Platelet count 75,000- <u>99,999</u> / $\mu$ L Second occurrence of platelet count 75,000- <u>99,999</u> / $\mu$ L	Revised to account for numerical overlap
- Restrictions During Study, #5	Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers	Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to receiving study drug <u>and/or</u> within 6 hours	Revised for consistency and precision

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
	within 48 hours of receiving study drug.	<u>after receiving</u> study drug.	
- Demographics and Baseline Characteristics	<ul style="list-style-type: none"> <li>• Race (<del>white, American Indian/Alaska native, Asian, native Hawaiian or other Pacific Islander, black/African American</del>)</li> </ul>	<ul style="list-style-type: none"> <li>• Race <u>(Asian, Black, Caucasian, Other, Unknown)</u></li> </ul>	Language revised for more inclusive race descriptors
- Subject Withdrawal Criteria	N/A	If a subject is lost to follow-up or withdraws from study treatment, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.	Additional information added to define sufficient attempts at follow-up.
- Study Drug Storage	The 100-mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 2°C to 30°C.	The 100-mg capsules (unlabeled active pharmaceutical ingredient) will be stored at <u>15°C</u> to <u>25°C</u> .	Storage conditions revised per current product storage conditions.
- Study Drug Administration	N/A	<u>Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration.</u>	Addition made to account for operational flexibility given the long fasting period required of subjects
- <b>Section 12.2 Adverse and</b>	<i>See below for original text</i>	<i>See below for revised text</i>	Updated for

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
Serious Adverse Events			consistency with other recent niraparib protocols.
<b>(ORIGINAL TEXT) Section 12.2 Adverse and Serious Adverse Events</b>			

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)	Rationale
<b>1.1. Adverse and Serious Adverse Events</b>			
<b>1.1.1. Definition of Adverse Events</b>			
<b>1.1.1.1. Adverse Event</b>			
<p>An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p> <p>All AEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by TESARO.</p> <p>Adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (version 16.1).</p>			
<b>1.1.1.2. Serious Adverse Event</b>			
<p>A serious adverse event (SAE) is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow up) and at any dose of the investigational product that fulfills one or more of the following:</p> <ul style="list-style-type: none"><li>• Results in death</li><li>• Is immediately life threatening</li><li>• Requires in-patient hospitalization or prolongation of existing hospitalization</li><li>• Results in persistent or significant disability or incapacity</li><li>• Results in a congenital abnormality or birth defect</li><li>• It is an important medical event that may jeopardize the subject and may require medical or surgical intervention or treatment to prevent 1 of the outcomes listed above.</li></ul> <p>Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc) will not be considered an</p>			

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)	Rationale
<p>SAE; however, any AE that prolongs hospitalization will be considered an SAE.</p> <p>All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by TESARO.</p>			
<h3><b>1.1.1.3. Suspected Unexpected Serious Adverse Reaction</b></h3> <p>Any AE that is serious, associated with the use of study drug, and unexpected (defined as not listed in the appropriate section of the current Investigator's Brochure [TESARO 2014]) is referred to as a suspected unexpected serious adverse reaction (SUSAR) and requires the following additional reporting requirements:</p> <ul style="list-style-type: none"><li>• If the SUSAR is fatal or life threatening, associated with the use of study drug, and unexpected, regulatory authorities, Institutional Review Boards (IRBs), and Independent Ethics Committees (IECs) will be notified within 7 calendar days after the Sponsor or designee learns of the event. Additional follow up information (cause of death, autopsy report, and hospital report) should be reported within an additional 8 calendar days (15 days total).</li><li>• If the SUSAR is not fatal or life threatening but is otherwise serious, associated with the use of study drug, and unexpected, regulatory authorities, IRBs, and IECs will be notified within 15 calendar days after the Sponsor or designee learns of the event.</li></ul> <p>The Sponsor or designee will notify the investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of subjects. Follow up information may be submitted, if necessary.</p> <p>The Sponsor or designee will also provide annual safety updates to the regulatory authorities, IRBs, and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.</p>			
<h2><b>1.2. Relationship to Study Drug</b></h2> <p>The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:</p> <ul style="list-style-type: none"><li>• Related: A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.</li></ul>			

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)	Rationale
<ul style="list-style-type: none"> <li>• <u>Likely related</u>: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.</li> <li>• <u>Unlikely to be related</u>: A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.</li> <li>• <u>Unrelated</u>: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.</li> </ul>			
<p>The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause and effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”</p>			
<h3>1.3. Recording Adverse Events</h3>			
<p>Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center. Clinically significant changes in laboratory values, blood pressure, and pulse rate need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from signing of the consent form until the end of the study. Serious AE information will be collected from signing of the consent form until 30 days following the last dose of study drug. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.</p>			
<p>Investigators should assess the severity of AEs according to CTCAE (<a href="#">HHS 2009</a>).</p>			
<p>In general, CTCAE version 4.02 severity grades are the following:</p>			
<ul style="list-style-type: none"> <li>• Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.</li> <li>• Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money,</li> </ul>			

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)	Rationale
<p>etc).</p> <ul style="list-style-type: none"> <li>Grade 3: Severe or medically significant but not immediately life threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).</li> <li>Grade 4: Life threatening consequences or urgent intervention indicated.</li> <li>Grade 5: Death related to AE.</li> </ul> <p>It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under <a href="#">Section 1.1.1.2</a>. An AE of severe intensity may not be considered serious.</p> <p>The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report form and reported to the PPD Pharmacovigilance Department staff at the SAE Hotline number at any time.</p> <p>Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.</p> <p>The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.</p> <p>Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.</p>			

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)	Rationale
<p>Pharmacovigilance Department staff at the SAE Hotline number at any time.</p>			
<p>Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the subject's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and faxed within 24 hours of receipt of the information. If a new SAE report form is faxed, then the Investigator must sign and date the form.</p>			
<p>The minimum information required for an initial report includes the following:</p> <ul style="list-style-type: none"><li>• Name of person sending the report (ie, name and address of Investigator)</li><li>• Patient identification (screening/randomization number, initials, and NOT the subject's name)</li><li>• Protocol number</li><li>• Description of SAE</li><li>• Causality assessment, if possible</li></ul>			
<p>However, as many points as possible on the SAE report form should be covered in the initial report, or the completed SAE report form itself must be faxed to the PPD Pharmacovigilance Department staff. In addition, the event must be documented in the eCRF.</p>			
<p>After receipt of the initial report, the safety center will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event.</p>			
<p>The Investigator and the Sponsor (or the Sponsor's designee) will review each SAE report, and the Sponsor or the Sponsor's designee will evaluate the seriousness and the causal relationship of the event to study drug. In addition, the Sponsor (or the Sponsor's designee) will evaluate the expectedness according to the Investigator's Brochure (<a href="#">TESARO 2014</a>). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.</p>			
<p>Additional follow up information, if required or available, should be faxed within 1 business day of receipt, and this follow up information should be completed on a follow up SAE form, placed with the original SAE information, and kept with the appropriate section of the eCRF and/or study file.</p>			
<p>TESARO is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB or IEC of all SAEs that occur at his or her study center.</p>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<b>(REVISED TEXT) Section 12.2 Adverse and Serious Adverse Events</b>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<b>1.1. Adverse and Serious Adverse Events</b>			
<b>1.1.1. <u>Definition of Adverse Events</u></b>			
<b>1.1.1.1. <u>Adverse Event</u></b>			
<p>An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p>			
<p>AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.</p>			
<p>Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.</p>			
<p>All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be documented.</p>			
<p>A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study treatment has been administered.</p>			
<b>1.1.1.2. <u>Serious Adverse Event</u></b>			
<p>An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:</p> <ul style="list-style-type: none"> <li>• <u>Results in death</u></li> <li>• <u>Is life-threatening</u> <ul style="list-style-type: none"> <li>– This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event</li> </ul> </li> </ul>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<u>hypothetically might have caused death if it were more severe</u>			
<ul style="list-style-type: none"> <li>• Requires inpatient hospitalization or prolongation of existing hospitalization</li> </ul>			
<ul style="list-style-type: none"> <li>• Results in persistent or significant disability or incapacity</li> </ul>			
<ul style="list-style-type: none"> <li>• Is a congenital anomaly or birth defect</li> </ul>			
<ul style="list-style-type: none"> <li>• Is an important medical event(s) <ul style="list-style-type: none"> <li>– An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.</li> </ul> </li> </ul>			
<p>Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.</p>			
<p>A distinction should be drawn between <u>serious</u> and <u>severe</u> AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.</p>			
<p>Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.</p>			
<p><b>1.1.1.3. Submission of Expedited Reports to Regulatory Authority, Sites, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)</b></p>			
<p>Per regulatory requirements, if an SAE report is required to be submitted to a Regulatory Authority a copy of this report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigators/site. TESARO or its designee will submit a copy of the report to their respective IRB or IEC.</p>			
<p><b>1.2. Relationship to Study Drug</b></p>			

Section(s)	Previous Text (deleted text shown by <u>strikethrough</u> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<p>The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:</p>			
<ul style="list-style-type: none"> <li>• Related: A clinical event, including a laboratory test abnormality, with a <u>plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals</u>. The response to withdrawal of the treatment should be clinically plausible.</li> <li>• Likely related: A clinical event, including a laboratory test abnormality, with a <u>reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals</u>.</li> <li>• Unlikely to be related: A clinical event, including a laboratory test abnormality, with a <u>temporal relationship to treatment administration that makes a causal relationship improbable</u>, and a concurrent disease or other drugs or chemicals provide <u>likely explanation</u>.</li> <li>• Unrelated: A clinical event, including a laboratory test abnormality, with <u>little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals</u>.</li> </ul>			
<p>The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”</p>			
<h3>1.3. Recording Adverse Events</h3>			
<p>AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see <a href="#">Table 1</a>, <a href="#">Table 2</a>, and <a href="#">Table 3</a> for schedules of events). All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.</p>			
<p>AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center.</p>			
<p>Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should</p>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<u>be recorded and reported according to the above SAE reporting process.</u>			
<u>Abnormal laboratory values that constitute an AE or SAE must be collected. Investigators should assess the severity of AEs according to CTCAE (<a href="#">HHS 2009</a>).</u>			
<u>In general, CTCAE version 4.02 severity grades are the following:</u>			
<ul style="list-style-type: none"> <li>• <u>Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.</u></li> <li>• <u>Grade 2: Minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).</u></li> <li>• <u>Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).</u></li> <li>• <u>Grade 4: Life-threatening consequences or urgent intervention indicated.</u></li> <li>• <u>Grade 5: Death related to AE.</u></li> </ul>			
<u>It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under <a href="#">Section 1.1.1.2</a>. An AE of severe intensity may not be considered serious.</u>			
<b>1.4. Reports of Pregnancy</b>			
<u>The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report notification form and reported to the Sponsor.</u>			
<u>Pregnancies occurring in subjects enrolled in a study or in a female partner of a male subject must be reported and followed to outcome. The Investigator is responsible for documenting the course and outcome of any pregnancy that occurs while a subject is enrolled in the study and any pregnancy that occurs within 90 days after a subject's last dose.</u>			
<u>Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered</u>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<p><u>an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.</u></p>			
<p><u>Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see <a href="#">Section 1.5</a>).</u></p>			
<p><u>The investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.</u></p>			
<p><u>The Investigator should follow-up with the subject or the subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.</u></p>			
<p><u>In the event the pregnancy outcome occurs after the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor, or designee, within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs.</u></p>			
<p style="text-align: center;"><b>PREGNANCY CONTACT INFORMATION</b></p> <p>Email: <u>PI</u> [REDACTED]</p> <p>Fax: <u>PI</u> [REDACTED]</p> <p>Telephone: <u>PI</u> [REDACTED]</p>			
<p><b>1.5. Reporting Adverse Events</b></p> <p>The Investigator must report any SAE once he/she becomes aware of within 24 hours of becoming aware of the event. SAEs must be reported using the following contact information:</p>			
<p style="text-align: center;"><b>SAE REPORTING CONTACT INFORMATION</b></p> <p>Email: <u>PI</u> [REDACTED]</p>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		Fax: <u>PI</u> Telephone: <u>PI</u>	
<p>For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report Form must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.</p>			
<p>Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the subject's personal identifiers (eg, subject name, medical record number) removed according to local regulations. The Investigator must sign and date all SAE forms.</p>			
<p><i>The minimum information required for an initial SAE report is:</i></p>			
<ul style="list-style-type: none"> <li>• <u>Name of person sending the report (ie, name, address of Investigator)</u></li> <li>• <u>Subject identification (screening/randomization number, initials, NOT subject name)</u></li> <li>• <u>Protocol number</u></li> <li>• <u>Description of SAE</u></li> <li>• <u>Causality assessment</u></li> </ul>			
<p>In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).</p>			
<p>After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to</p>			

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<u>obtain further information</u>			
- Appendices, <a href="#">Table 12</a>	N/A	<p><u>CredibleMeds</u> web site.  <a href="https://www.crediblemeds.org">https://www.crediblemeds.org</a></p> <p><u>US Pharmacist</u> web site. <u>Drug-induced QT prolongation</u> page. Available at:  <a href="http://www.uspharmacist.com/content/d/featured_articles/c/10396/">http://www.uspharmacist.com/content/d/featured_articles/c/10396/</a>. Accessed 12 November 2013.</p> <p><u>Cardiac Risk in the Young</u> sponsored web site on <u>Sudden Arrhythmic Death Syndrome</u>. Available at:  <a href="http://www.sads.org.uk/drugs_to_avoid.htm">http://www.sads.org.uk/drugs_to_avoid.htm</a>. Accessed 24 October 2014.</p>	Additional References provided
General	<del>PPD Pharmacovigilance Department</del>	<u>DSA</u>	Vendor for reporting serious adverse events has changed.
- List of References	N/A	<p><u>Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, et al.</u> Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. <i>J Clin Oncol.</i> 2001;19(5):1519-38.</p> <p><u>Slichter SJ.</u> Evidence-based platelet transfusion guidelines. <i>Hematology Am Soc Hematol Educ Program.</i> 2007:172-8. [stet, per PubMed]</p>	Reference added for dose adjustment criteria.



## Summary of Protocol Changes

### Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

Previous Version: Version 1.0, dated 28 May 2014

Current Version: Amendment 1, Version 2.0, dated 01 December 2014

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
Global	N/A	Minor grammatical, typographical, and/or formatting/style errors and inconsistencies were corrected, including (but not limited to): replacing spelled numbers with numerals, adding articles before abbreviations, adding/removing hyphens, updating list of abbreviations, adjusting spacing after periods	Editorial changes were made throughout to improve clarity and flow, as well as maintain a consistent style.
Global	N/A	Various unsubstantial changes were made, ie, those which are unlikely to have a significant impact on the safety, physical, or mental integrity of the subjects; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of the investigational product.	Provide increased clarity to the study protocol. These changes will be documented in detail in the redline version of the final protocol.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
Global	N/A	Two spaces after periods were replaced with one space.	Spacing change was made to maintain a consistent style across sponsor programs.
- List of abbreviations - Global - Tables/Figures	N/A	In the list of abbreviations, rows were deleted and added. In the body text, abbreviation definitions and usage were revised as needed. In Tables/Figures, lists of abbreviations were added as needed.	Abbreviations were changed to provide additional definitions and improve clarity.
Global	TESARO	<u>The Sponsor</u>	“TESARO” was replaced with “the Sponsor” so that Tesaro is referred to in the same way throughout the document.
Global	<del>Treatment discontinuation</del>	<u>End of Treatment (EOT)</u>	“treatment discontinuation” was replaced with “end of treatment” (or EOT) for consistency with other Tesaro protocols.
- Title page - Document headers and footers	N/A	Amendment number and date were updated. Headers and footers were updated.	Changed to reflect Amendment 1 information. Headers and footers updated per new Regulatory style.
- Sponsor signature page	PI [REDACTED] PhD <del>Chief Medical Officer</del>	PI [REDACTED] MD <u>Senior Medical Director</u>	The responsible medical expert for the sponsor was updated to reflect a personnel change made by the sponsor.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
- Synopsis, Name of Active Ingredient	<del>(3S)-3-[4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl] piperidine (tosylate monohydrate salt)</del>	<u>Niraparib</u>	Changed to the international nonproprietary name for consistency with other protocols.
- Synopsis, Study Period (years)	Estimated first subject enrolled: <del>December 2014</del>	<u>February 2015</u>	Date changed to reflect current enrollment expectations.
- Synopsis, Methodology, Part 1 - Synopsis, Methodology, Part 2 <b>- 7.1 Overall Study Design, Part 1</b> <b>- 7.1 Overall Study Design, Part 2</b>	After <del>the Screening Visit (occurring</del> within the 3 weeks prior to study drug administration), subjects <del>will be admitted to the study center the afternoon prior to study drug administration (ie, Study Day -1, at least 12 hours prior to study drug administration).</del>	The Screening Visit <u>will occur</u> within the 3 weeks prior to study drug administration. <u>All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.</u>	To allow for operational flexibility, Day -1 criteria modified to account for optional overnight stay.
- 7.1 Overall Study Design, Part 1 - 7.1 Overall Study Design, Part 2	N/A	<u>Water is permissible during the overnight fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration.</u>	Addition made to account for operational flexibility given the long fasting period required of subjects.
- Synopsis, Methodology, Extension study - 7.1 Overall Study Design, Extension study	On the same day that subjects complete Part 1 or 2 of the study, subjects <del>will</del> be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments.	On the same day that subjects complete Part 1 or 2 of the study, subjects <u>may</u> be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments.	Changed to clarify that enrollment in the extension study is contingent upon meeting inclusion/exclusion criteria.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
- Synopsis, Methodology, Extension study - 7.1 Overall Study Design, Extension study	Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ( <u>Section</u> ).	Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria ( <u>Section 8.4</u> ), <u>or until the subject can be transitioned to the roll-over study (if eligible, see below)</u> .	Changes made to clarify the difference between the main study vs. extension study vs. roll-over study.
- Synopsis, Methodology, Roll-over study - 7.1 Overall Study Design, Roll-over study	N/A	<b><u>Roll-over study (all eligible subjects):</u></b> <u>Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.</u>	Additions made to clarify the difference between the main study vs. extension study vs. roll-over study.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Inclusion #6	N/A	<u>Female subjects of childbearing potential must have a negative serum pregnancy test (beta hCG) within 72 hours prior to receiving the first dose of study drug.</u>	Addition made to clarify the need for a negative serum pregnancy test prior to enrollment.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Inclusion #7	Male and female subjects of <del>childbearing</del> potential must use adequate birth control for the duration of study participation (Section 8.3).	Male and female subjects of <u>reproductive</u> potential must use adequate birth control for the duration of study participation ( <u>Section 8.3</u> ).	Re-worded to account for need for male birth control
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #1	Subject has undergone palliative radiotherapy within 1 week of the Screening Visit, encompassing >20% of the bone marrow.	Subject has undergone palliative radiotherapy within 1 week of <u>study drug administration</u> , encompassing >20% of the bone marrow.	Radiotherapy may not have occurred within one week of study drug administration, not within one week of the screening visit.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #5	Subject has had major surgery within 3 weeks of <del>the Screening Visit</del> or has not recovered from all effects of any major surgery.	Subject has had major surgery within 3 weeks of <u>study drug administration</u> or has not recovered from all effects of any major surgery.	Major surgery may not have occurred within three weeks of study drug administration, not within three weeks of the screening visit.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #7	N/A	<u>Subject received a transfusion (platelets or red blood cells) within 4 weeks of study drug administration.</u>	Additional exclusion criterion for consistency with other niraparib studies.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion #14	Subject is starting chemotherapy within 3 weeks of <del>the Screening Visit</del> .	Subject is starting chemotherapy within 3 weeks of <u>study drug administration</u> .	Chemotherapy may not have occurred within three weeks of study drug administration, not within three weeks of the screening visit.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion # 16	Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours of study drug administration.	Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, <u>and/or within 6 hours after study drug administration.</u>	Detail added to clarify use of the indicated medications following study drug administration
General	N/A	<u>IB version 3.0, 09 April 2014</u>	Added IB version number and date for precision and clarity.
- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion # 17	Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to <del>the Screening Visit</del> ) or dependence or is unable to abstain from alcohol for the duration of the study.	Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to <u>study drug administration</u> ) or dependence or is unable to abstain from alcohol for the duration of the study.	Chronic alcohol use may not have occurred within 30 days prior to study drug administration, not within 30 days prior to the screening visit.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
- Overall Study Design, <a href="#">Table 2</a> , <a href="#">Table 3</a> , <a href="#">Table 4</a>	N/A	Moved to immediately after Synopsis (Section 2)	Ethics Committee request
- Overall Study Design, <a href="#">Table 2</a>	<i>See below for original table</i>	<i>See below for revised table</i>	Updated per discussions: - Serum pregnancy test at screening and at EOT. - ECOG performance test at screening and EOT - PK blood sample windows updated - Oral temperature changed to aural/tympanic - Footnotes updated as described herein.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )		Revised and/or Updated text (added text shown by <u>underline</u> )										Rationale										
<b>(ORIGINAL) Table 2: Schedule of Assessments: Part 1</b>																							
Assessment or Procedure	Day Relative to First Dose of Study Drug												<b>End of Part 1</b>										
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22										
Informed consent	X																						
Subject demographics and baseline characteristics	X																						
Medical history and cancer history	X																						
Inclusion/exclusion criteria	X																						
Physical examination	X												X										
Height (cm)	X																						
Weight (kg)	X	X											X										
Body mass index (kg/m <sup>2</sup> )	X																						
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X										
HBV/HCV/HIV screening <sup>c</sup>	X																						
Clinical laboratory assessments <sup>d</sup>	X	X					X						X										
Serum pregnancy test	X																						
Electrocardiogram (12-lead) <sup>e</sup>	X		X										X										
ECOG performance status	X																						
Confirm diagnosis with CT scan <sup>f</sup>	X																						
Screening number assignment	X																						
Subject confinement		X	X	X	X	X																	

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )			Revised and/or Updated text (added text shown by <u>underline</u> )								Rationale			
Subject dosing number assignment															
Niraparib oral administration <sup>g</sup>															
[ <sup>14</sup> C]-niraparib IV infusion <sup>h</sup>															
Pharmacokinetic blood sampling <sup>i</sup>				X	X	X	X	X	X	X	X	X	X		
Prior/concomitant medication and AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous.

<sup>a</sup> Subjects ~~will be admitted to the study center the afternoon prior to study drug administration (at least 12 hours prior to study drug administration).~~

<sup>b</sup> Vital signs include blood pressure, pulse rate, and ~~oral~~ temperature. ~~Vital signs will be collected prior to study drug administration on Day 1 and prior to any blood draws on other study days.~~

<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>d</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. On Day 1, blood samples should be drawn prior to study drug administration.

<sup>e</sup> Subjects will have a 12-lead electrocardiogram at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>f</sup> ~~Subjects must provide a CT scan to confirm their diagnosis. A CT scan is performed every 8 weeks as part of standard of care.~~

<sup>g</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.

<sup>h</sup> A 15-minute IV infusion of 100 µg [<sup>14</sup>C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.

<sup>i</sup> Blood samples for pharmacokinetic analysis will be collected at the following times: predose (0 hour), Day 1 (1, 1.5, 2 [prior to IV infusion], 2.125, 2.25, 2.33, 2.66, 3, 4, 6, and 12 [ $\pm$ 4] hours postdose), Day 2 (24 [ $\pm$ 1] hours postdose), Day 3 (48 [ $\pm$ 2] hours postdose), Day 4 (72 [ $\pm$ 4] hours postdose), Day 5 (96 [ $\pm$ 4] hours postdose), Day 7 (144 [ $\pm$ 4] hours postdose), Day 9 (192 [ $\pm$ 8] hours postdose), Day 11 (240 [ $\pm$ 12] hours postdose), Day 13 (288 [ $\pm$ 12] hours postdose), Day 15 (336 [ $\pm$ 12] hours postdose), and Day 22 (504 [ $\pm$ 12] hours postdose).

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )											Rationale
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**(REVISED) Table 2: Schedule of Assessments: Part 1**

Assessment or Procedure	Day Relative to First Dose of Study Drug												
	-21 to -2 Screening Visit	-1 <sup>a</sup>	1	2	3	4	5	7	9	11	13	15	22 End of Part 1
Informed consent	X												
Subject demographics and baseline characteristics	X												
Medical history and cancer history	X												
Inclusion/exclusion criteria	X												
Physical examination	X												X
Height (cm)	X												
Weight (kg)	X	X											X
Body mass index (kg/m <sup>2</sup> )	X												
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>c</sup>	X												
Clinical laboratory assessments <sup>d</sup>	X	X											X
Serum pregnancy test ( <u>women of childbearing potential</u> )	X												X <sup>e</sup>
Electrocardiogram (12-lead) <sup>f</sup>	X		X										X
ECOG performance status	X												X <sup>e</sup>
Confirm diagnosis with CT scan <sup>g</sup>	X												
Subject confinement		X <sup>h</sup>	X	X	X	X	X						

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )				Revised and/or Updated text (added text shown by <u>underline</u> )						Rationale	
Niraparib oral administration <sup>i</sup>			X									
[ <sup>14</sup> C]-niraparib IV infusion <sup>j</sup>			X									
Pharmacokinetic blood sampling <sup>k</sup>			X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X <sup>e</sup>
Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous												
<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.												
<sup>b</sup> Vital signs include blood pressure, pulse rate, and <u>aural (tympanic)</u> temperature. On Day 1, vital signs <u>should</u> be collected prior to study drug administration.												
<sup>c</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.												
<sup>d</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.												
<sup>e</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see <a href="#">Section 1.3</a> ).												
<sup>f</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.												
<sup>g</sup> <u>Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.</u>												
<sup>h</sup> <u>If subject chooses to be admitted on Day -1.</u>												
<sup>i</sup> Subjects will receive a single, 300-mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) oral dose of niraparib after an overnight fast of at least 10 hours.												
<sup>j</sup> A 15-minute IV infusion of 100 µg [ <sup>14</sup> C]-niraparib will start 2 hours after administration of the niraparib oral dose. Subjects will continue fasting until 2 hours after the start of the IV infusion.												
<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour within <u>30 min prior to dose</u> ), Day 1 (1 [ $\pm 2$ min], 1.5 [ $\pm 2$ min], 2 [prior to IV infusion], 2.125 [ $\pm 1$ min], 2.25 ( <u>immediately after infusion</u> ), 2.33 [ $\pm 1$ min], 2.66 [ $\pm 1$ min], 3 [ $\pm 2$ min], 4 [ $\pm 5$ min], 6 [ $\pm 5$ min], and 12 hours [ $\pm 15$ min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 7 (144 [ $\pm 4$ ] hours postdose), Day 9 (192 [ $\pm 8$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 13 (288 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).												
<sup>l</sup> <u>Serious adverse events (SAEs) will be recorded up to 30 days after EOT.</u>												

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
- Overall Study Design, Table 2	<i>See below for original table</i>	<i>See below for revised table</i>	Updated as per discussion: - Subject confinement not necessary on day -1 - Serum pregnancy test at screening and at EOT. - ECOG performance test at screening and EOT - PK and metabolite blood sample windows updated - Oral temperature changed to aural/tympanic - Footnotes updated as described herein.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )		Revised and/or Updated text (added text shown by <u>underline</u> )															Rationale
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**(ORIGINAL) Table 3: Schedule of Assessments: Part 2**

Assessment or Procedure	Day Relative to First Dose of Study Drug																		
	-21 to -2	-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup> End of Part 2	
Informed consent	X																		
Subject demographics and baseline characteristics	X																		
Medical history and cancer history	X																		
Inclusion/exclusion criteria	X																		
Physical examination	X																	X	
Height (cm)	X																		
Weight (kg)	X	X																X	
Body mass index (kg/m <sup>2</sup> )	X																		
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
HBV/HCV/HIV screening <sup>d</sup>	X																		
Clinical laboratory assessments <sup>e</sup>	X	X																X	X
Serum pregnancy test	X																		
Electrocardiogram (12-lead) <sup>f</sup>	X		X															X	
ECOG performance status	X																		
Confirm diagnosis with CT scan <sup>g</sup>	X																		
Screening number assignment	X																		

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )										Revised and/or Updated text (added text shown by <u>underline</u> )										Rationale				
Subject confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X										
Subject dosing number assignment			X																						
[ <sup>14</sup> C]-niraparib administration <sup>h</sup>			X																						
Pharmacokinetic blood sampling <sup>i</sup>			X	X	X	X	X	X			X												X	X	
Blood sample for metabolite profiling <sup>j</sup>			X	X	X	X	X	X			X												X	X	
Urine collection <sup>k</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Fecal collection <sup>l</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior/concomitant medication and AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X		

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

<sup>a</sup> Subjects will be admitted to the study center the afternoon prior to study drug administration (at least 12 hours prior to study drug administration).

<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote k and Footnote l), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped.

<sup>c</sup> Vital signs include blood pressure, pulse rate, and ~~oral~~ temperature. Vital signs will be collected prior to study drug administration on Day 1 and prior to any blood draws on other study days.

<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.

<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. On Day 1, blood samples should be drawn prior to study drug administration.

<sup>f</sup> Subjects will have a 12-lead electrocardiogram at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.

<sup>g</sup> Subjects must provide a CT scan to confirm their diagnosis. ~~A CT scan is performed every 8 weeks as part of standard of care.~~

<sup>h</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 µCi of radioactivity, after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.

<sup>i</sup> Blood samples for pharmacokinetic analysis will be collected at the following times: predose (0 hour), Day 1 (1, 1.5, 2, 3, 4, 6, and 12 [ $\pm$ 1] hours postdose), Day 2 (24 [ $\pm$ 1] hours postdose), Day 3 (48 [ $\pm$ 2] hours postdose), Day 4 (72 [ $\pm$ 4] hours postdose), Day 5 (96 [ $\pm$ 4] hours postdose), Day 6 (120 [ $\pm$ 4] hours postdose), Day 8 (168 [ $\pm$ 4] hours postdose), Day 11 (240 [ $\pm$ 12] hours postdose), Day 15 (336 [ $\pm$ 12] hours postdose), and Day 22 (504 [ $\pm$ 12] hours postdose).

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
<sup>j</sup>	Blood samples for metabolite profiling will be collected at the following times: predose (0 hour), Day 1 (1, 2, 3, 6, and 12 [ $\pm 1$ ] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).		
<sup>k</sup>	Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.		
<sup>l</sup>	Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.		

**(REVISED) Table 3: Schedule of Assessments: Part 2**

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )						Revised and/or Updated text (added text shown by <u>underline</u> )						Rationale						
Assessment or Procedure	-21 to -2 Screening Visit	Day Relative to First Dose of Study Drug																	
		-1 <sup>a</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22 <sup>b</sup> End of Part 2	
Informed consent	X																		
Subject demographics and baseline characteristics	X																		
Medical history and cancer history	X																		
Inclusion/exclusion criteria	X																		
Physical examination	X																	X	
Height (cm)	X																		
Weight (kg)	X	X																X	
Body mass index (kg/m <sup>2</sup> )	X																		
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
HBV/HCV/HIV screening <sup>d</sup>	X																		
Clinical laboratory assessments <sup>e</sup>	X	X															X	X	
Serum pregnancy test ( <u>women of childbearing potential</u> )	X																	X <sup>f</sup>	
Electrocardiogram (12-lead) <sup>g</sup>	X		X																X
ECOG performance status	X																	X <sup>f</sup>	
Confirm diagnosis with CT scan <sup>h</sup>	X																		
Subject confinement		X <sup>i</sup>	X	X	X	X	X	X	X	X	X	X	X	X					
[ <sup>14</sup> C]-niraparib administration <sup>j</sup>			X																

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )							Revised and/or Updated text (added text shown by <u>underline</u> )							Rationale		
Pharmacokinetic blood sampling <sup>k</sup>		X	X	X	X	X	X	X		X			X			X	X
Blood sample for metabolite profiling <sup>l</sup>		X	X	X	X	X	X	X		X			X			X	X
Urine collection <sup>m</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal collection <sup>n</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication and AE monitoring <sup>o</sup>	X	X	X	X	X	X	X	X	X	X	X	X			X	X <sup>f</sup>	
Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.																	
<sup>a</sup> All subjects must report to the study center on the day prior to study drug administration (Day -1) for study events. Subjects have the option of staying overnight at the study center on Day -1. Subjects not staying at the study center on Day -1 must report back to the study center at least 2 hours prior to study drug administration.																	
<sup>b</sup> Due to the possibility that urine and fecal samples may need to be collected beyond Day 22 (see Footnote m and Footnote n), participation in Part 2 of the study may extend beyond Day 22. Subjects will be eligible for the extension study once collection of urine and fecal samples has stopped.																	
<sup>c</sup> Vital signs include blood pressure, pulse rate, and <u>aural (tympanic)</u> temperature. On Day 1, vital signs should be collected prior to study drug administration.																	
<sup>d</sup> Testing for HBV, HCV, and HIV will only be performed at the Screening Visit if there is suspicion of infection. If the subject tests positive for HBV, HCV, and/or HIV, the subject will not be eligible to participate in the study.																	
<sup>e</sup> Hematology assessments include the following: hemoglobin, platelets, white blood cells, differential white cell count, activated partial thromboplastin time, and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, AST, ALT, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase.																	
<sup>f</sup> All subjects who do not enroll in the extension study must have a serum pregnancy test and ECOG performance status assessment prior to study exit. Discontinued subjects will be followed for all relevant safety parameters (see <a href="#">Section 12.4</a> ).																	
<sup>g</sup> Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.																	
<sup>h</sup> Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.																	
<sup>i</sup> If subject chooses to be admitted on Day -1.																	
<sup>j</sup> Subjects will receive a single, 300-mg oral dose of niraparib, containing approximately 100 $\mu$ Ci of radioactivity ( <u>3 × 100-mg capsules, labeled active pharmaceutical ingredient [3 × 33.3 <math>\mu</math>Ci of radioactivity]</u> ), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.																	
<sup>k</sup> Blood samples for PK analysis will be collected at the following times: predose (0 hour, <u>within 30 min prior to dose</u> ), Day 1 (1 [ $\pm 2$ min], 1.5 [ $\pm 2$ min], 2 [ $\pm 2$ min], 3 [ $\pm 2$ min], 4 [ $\pm 5$ min], 6 [ $\pm 5$ min], and 12 hours [ $\pm 15$ min] postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).																	

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<sup>l</sup>	Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, <del>within 30 min prior to dose</del> ), Day 1 (1 [ $\pm 2$ min], 2 [ $\pm 2$ min], 3 [ $\pm 2$ min], 6 [ $\pm 5$ min], and 12 [ $\pm 15$ min] hours postdose), Day 2 (24 [ $\pm 1$ ] hours postdose), Day 3 (48 [ $\pm 2$ ] hours postdose), Day 4 (72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).		
<sup>k</sup>	Urine samples will be collected for Part 2 prior to study drug administration (0 hour); in block collections from 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours postdose; and then in block collections every 24 hours. The compound-derived radioactivity in the urine will be quantified at the study center. When subjects are not confined to the study center, urine samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 urine sample is detected to be higher than 0.1% of the radioactivity of the dose given, urine samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, urine samples will continue to be collected every 24 hours on a weekly schedule.		
<sup>l</sup>	Fecal samples will be collected for Part 2 prior to study drug administration (0 hour) and then all bowel movements will be collected in 24-hour blocks, with 1 stool per container. The compound-derived radioactivity in the feces will be quantified at the study center. When subjects are not confined to the study center, fecal samples will be collected via courier service every 24 hours. If the total radioactivity in the Day 15 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 22. If the total radioactivity in the Day 22 fecal sample is detected to be higher than 0.1% of the radioactivity of the dose given, fecal samples will be collected every 24 hours through Day 29. As long as the radioactivity remains higher than 0.1% of the dose given, fecal samples will continue to be collected every 24 hours on a weekly schedule.		
<sup>o</sup>	<u>SAEs will be recorded up to 30 days after EOT.</u>		
- Overall Study Design, Table 3	<i>See below for original table</i>	<i>See below for revised table</i>	Updated as per discussion: - Serum pregnancy test at screening and at EOT. - ECOG performance test at screening and EOT - PK blood sample windows updated - Oral temperature changed to aural/tympanic - Footnotes updated as described herein.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<b>(ORIGINAL) Table 4: Schedule of Assessments: Open-label Extension Study</b>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )		Revised and/or Updated text (added text shown by <u>underline</u> )				Rationale
Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b,c</sup>	Treatment Discontinuation <sup>d</sup>
		Day 1	Day 8	Day 15	Day 21		
Inclusion/exclusion criteria <sup>e</sup>	X	✗					
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>f</sup>	X	✗	X	X	X	X	X
Complete blood count <sup>g</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>h</sup>	X			X		X	X
Pregnancy test <sup>i</sup>	X					X	X
Study drug dispensed/collected <sup>j</sup>		✗				X	X
Electrocardiogram (12-lead) <sup>k</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>l</sup>		X				X	X
Concomitant medication and AE monitoring <sup>m</sup>	X	X	X	X	✗	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> On the same day that subjects complete Part 1 or 2 of the study, subjects will be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in [Table 6](#). Subjects have 7 days to complete the screening assessments, and the Screening Visit (+7 days) and Cycle 1/Day 1 Visit can occur on the same day.

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days.

<sup>c</sup> Visits will continue approximately every 4 weeks until treatment discontinuation.

<sup>d</sup> The visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria.

<sup>e</sup> If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the inclusion/exclusion criteria should only be reviewed once.

<sup>f</sup> Vital signs include blood pressure, pulse rate, and oral temperature. Vital signs will be collected prior to study drug administration and blood draws. If the

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
	Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.		
<sup>g</sup>	The <del>complete blood count</del> includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.		
<sup>h</sup>	Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.		
<sup>i</sup>	A urine pregnancy test will be conducted at the Screening Visit and every 3 months thereafter. A serum pregnancy test will be conducted at treatment discontinuation.		
<sup>j</sup>	Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. No new capsules will be dispensed at treatment discontinuation.		
<sup>k</sup>	Subjects will have a 12-lead electrocardiogram at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at treatment discontinuation.		
<sup>l</sup>	Blood samples for pharmacokinetic analysis will be collected at the following times: Cycle 1/Day 1 Visit (predose and 2 hours postdose), Cycle 2/Day 1 Visit (predose and 2 hours postdose), Cycle 4/Day 1 Visit (predose), and Cycle 8/Day 1 Visit (predose).		
<sup>m</sup>	Serious AEs will be recorded up to 30 days after treatment discontinuation.		
<b>(REVISED) Table 4: Schedule of Assessments: Open-label Extension Study</b>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )		Revised and/or Updated text (added text shown by <u>underline</u> )				Rationale
Assessment or Procedure	Screening Visit <sup>a</sup> (+7 days)	Cycle 1 <sup>b</sup>				Cycle n <sup>b</sup>	EOT <sup>c</sup>
		Day 1	Day 8	Day 15	Day 22	Day 1	
Inclusion/exclusion criteria	X						
Physical examination		X		X		X	X
Weight (kg)	X			X		X	X
Vital signs <sup>d</sup>	X	X	X	X	X	X	X
Complete blood count (CBC) <sup>e</sup>	X		X	X	X	X	X
Coagulation and blood chemistry <sup>f</sup>	X			X		X	X
Pregnancy test (women of childbearing potential) <sup>g</sup>	X					X	X
Study drug dispensed/collected <sup>h</sup>		X				X	X
Electrocardiogram (12-lead) <sup>i</sup>		X				X	X
ECOG performance status	X					X	X
Pharmacokinetic blood sampling <sup>j</sup>		X				X	X
Concomitant medication and AE monitoring <sup>k</sup>	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> Upon completion of Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in **Error! Reference source not found.** Subjects have 7 days to complete the screening assessments. The Screening Visit should occur within 1 and 7 days after the last dose of study drug (Part 1 or Part 2). The Cycle 1/Day 1 Visit can occur on the same day as the Screening Visit.

<sup>b</sup> Treatment cycles are 28 ( $\pm 3$ ) days. Visits (except Cycle 1) will continue approximately every 4 weeks until treatment discontinuation

<sup>c</sup> The EOT visit should occur within 7 days of the last dose of study drug. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria. If the subject discontinues due to disease progression, then the CT scan (taken per standard of care) closest to the time of progression (EOT) should be provided.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<sup>f</sup>	Vital signs include blood pressure, pulse rate, and <u>aural (tympanic)</u> temperature. On Day 1, vital signs should be collected prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the vital signs should only be collected once.		
<sup>e</sup>	The <u>CBC</u> includes hemoglobin, platelets, white blood cells, and neutrophils. Blood samples should be drawn prior to study drug administration. If the Screening Visit and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.		
<sup>f</sup>	Coagulation assessments include activated partial thromboplastin time and international normalized ratio. Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase <u>AST</u> , alanine aminotransferase <u>ALT</u> , blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase. Blood samples should be drawn prior to study drug administration. If the Screening Visit (+7 days) and Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed prior to study drug administration.		
<sup>g</sup>	<u>A serum pregnancy test will be conducted at the Screening Visit and at EOT. A urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.).</u>		
<sup>h</sup>	Subjects will take 300 mg (3 × 100-mg capsules, unlabeled active pharmaceutical ingredient) of oral niraparib daily. <u>No fasting period is required during the extension study.</u> Dose interruption (no longer than 28 days) will be allowed based on treatment side effects. In addition, dose reductions to 200 mg (2 × 100-mg capsules) QD and subsequently to 100 mg (1 × 100-mg capsule) QD will be allowed based on treatment side effects. Dose interruptions or reductions will not affect the timing and completion of study assessments. No new capsules will be dispensed at EOT.		
<sup>i</sup>	Subjects will have a 12-lead ECG at the Day 1 Visit (predose and 2 hours postdose) for each cycle and at <u>EOT</u> .		
<sup>j</sup>	Blood samples for PK analysis will be collected at the following times: Cycle 1/Day 1 Visit ( <u>within 30 min</u> predose and 2 hours <u>±15 min</u> postdose), Cycle 2/Day 1 Visit ( <u>within 30 min</u> predose and 2 hours <u>±15 min</u> postdose), Cycle 4/Day 1 Visit ( <u>within 30 min</u> predose), and Cycle 8/Day 1 Visit ( <u>within 30 min</u> predose).		
<sup>k</sup>	SAEs will be recorded up to 30 days after EOT.		
<ul style="list-style-type: none"> <li>- Synopsis, Methodology, Diagnosis and main criteria for inclusion, Exclusion # 18</li> </ul>	Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of <u>the Screening Visit</u> .	Subject is currently participating in another clinical study or has participated in a clinical study within 21 days of <u>study drug administration</u> .	Participation in another clinical trial may not have occurred within 21 days of study drug administration, not within 21 days of the screening visit.
<ul style="list-style-type: none"> <li>- Overall Study Design, Table 2, Table 3, Table 4</li> <li>- Safety Parameters, Vital Signs</li> </ul>	<p>Vital signs include blood pressure, pulse rate, and <u>oral</u> temperature.</p> <p><u>Vital signs will be collected prior to study drug administration on Day 1 and prior to any blood draws on other study days.</u></p>	<p>Vital signs include blood pressure, pulse rate, and <u>aural (tympanic)</u> temperature.</p> <p><u>On Day 1, vital signs should be collected prior to study drug administration.</u></p>	Not necessary to define when vital signs are to be collected in visits that occur after study drug administration.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
- Medical History and Cancer History	Subjects must provide a <del>previous</del> CT scan to confirm their cancer diagnosis. A <del>CT scan is performed every 8 weeks as part of standard of care.</del>	Subjects must provide <u>the most recent</u> CT scan ( <u>taken prior to enrollment</u> ) to confirm their cancer diagnosis. <u>CT scans should be performed per standard of care.</u> <u>If the subject discontinues due to disease progression, then the CT scan closest to the time of progression (EOT) should also be provided.</u>	Clarifications and revisions made per medical input.
- Overall Study Design, Tables 1 and 2 - Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling	Blood samples for pharmacokinetic analysis will be collected at the following times: predose (0 hour), Day 1 (1, 1.5, 2 [ <del>prior to IV infusion</del> ], 2.125, 2.25, 2.33, 2.66, 3, 4, 6, and 12 [ <del>±1 hours</del> ] postdose), Day 2 (24 [ <del>±1</del> ] hours postdose), Day 3 (48 [ <del>±2</del> ] hours postdose), Day 4 (72 [ <del>±4</del> ] hours postdose), Day 5 (96 [ <del>±4</del> ] hours postdose), Day 7 (144 [ <del>±4</del> ] hours postdose), Day 9 (192 [ <del>±8</del> ] hours postdose), Day 11 (240 [ <del>±12</del> ] hours postdose), Day 13 (288 [ <del>±12</del> ] hours postdose), Day 15 (336 [ <del>±12</del> ] hours postdose), and Day 22 (504 [ <del>±12</del> ] hours postdose).	Blood samples for PK analysis will be collected at the following times: predose (0 hour, <u>within 30 min prior to dose</u> ), Day 1 (1 [ <u>±2 min</u> ], 1.5 [ <u>±2 min</u> ], 2 [ <u>±2 min</u> ], 3 [ <u>±2 min</u> ], 4 [ <u>±5 min</u> ], 6 [ <u>±5 min</u> ], and 12 hours [ <u>±15 min</u> ] postdose), Day 2 (24 [ <del>±1</del> ] hours postdose), Day 3 (48 [ <del>±2</del> ] hours postdose), Day 4 (72 [ <del>±4</del> ] hours postdose), Day 5 (96 [ <del>±4</del> ] hours postdose), Day 6 (120 [ <del>±4</del> ] hours postdose), Day 8 (168 [ <del>±4</del> ] hours postdose), Day 11 (240 [ <del>±12</del> ] hours postdose), Day 15 (336 [ <del>±12</del> ] hours postdose), and Day 22 (504 [ <del>±12</del> ] hours postdose).	Sampling windows revised for consistency and precision
- Overall Study Design, Table 2 - Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling	Blood samples for metabolite profiling will be collected at the following times: predose (0 hour), Day 1 (1, 2, 3, 6, and 12 [ <del>±1</del> ] hours postdose), Day 2 (24 [ <del>±1</del> ] hours postdose), Day 3 (48 [ <del>±2</del> ] hours postdose), Day 4	Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, <u>within 30 min prior to dose</u> ), Day 1 (1 [ <u>±2 min</u> ], 2 [ <u>±2 min</u> ], 3 [ <u>±2 min</u> ], 6 [ <u>±5 min</u> ], and 12 [ <u>±15 min</u> ] hours postdose), Day 2 (24 [ <del>±1</del> ] hours postdose), Day 3 (48 [ <del>±2</del> ] hours postdose), Day 4 (72 [ <del>±4</del> ] hours postdose)	Sampling windows revised for consistency and precision

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <del>strikethrough</del> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
	(72 [ $\pm 4$ ] hours postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).	postdose), Day 5 (96 [ $\pm 4$ ] hours postdose), Day 6 (120 [ $\pm 4$ ] hours postdose), Day 8 (168 [ $\pm 4$ ] hours postdose), Day 11 (240 [ $\pm 12$ ] hours postdose), Day 15 (336 [ $\pm 12$ ] hours postdose), and Day 22 (504 [ $\pm 12$ ] hours postdose).	
- Overall Study Design, Table 3 - Blood Sample Collection: Pharmacokinetic Assessments and Metabolite Profiling	Blood samples for pharmacokinetic analysis will be collected at the following times: Cycle 1/Day 1 Visit (predose and 2 hours postdose), Cycle 2/Day 1 Visit (predose and 2 hours postdose), Cycle 4/Day 1 Visit (predose), and Cycle 8/Day 1 Visit (predose).	Blood samples for PK analysis will be collected at the following times: Cycle 1/Day 1 Visit ( <u>within 30 min predose and 2 hours <math>\pm 15</math> min postdose</u> ), Cycle 2/Day 1 Visit ( <u>within 30 min predose and 2 hours <math>\pm 15</math> min postdose</u> ), Cycle 4/Day 1 Visit ( <u>within 30 min predose</u> ), and Cycle 8/Day 1 Visit ( <u>within 30 min predose</u> ).	Sampling windows revised for consistency and precision
- Overall Study Design, Table 4	A <del>urine</del> pregnancy test will be conducted at the Screening Visit and <del>every 3 months thereafter. A serum pregnancy test will be conducted at treatment discontinuation.</del>	A <u>serum</u> pregnancy test will be conducted at the Screening Visit and <u>at EOT</u> . A <u>urine pregnancy test will be conducted every 3 months for the duration of the study (ie, Cycle 4, Cycle 7, etc.)</u> .	Corrected timing of serum vs. urine pregnancy tests, and clarified frequency of the tests.
- Overall Study Design, Table 2, Table 3	N/A	All subjects who do not enroll in the <u>extension study must have a serum pregnancy test and ECOG prior to study exit. Discontinued subjects will be followed for safety per section 12.4.</u>	Revised to include additional study exit criteria for any patients who do not enroll in the extension study.

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
- Dose Adjustment Criteria, Table 6	Platelet count 75,000-100,000/ $\mu$ L Second occurrence of platelet count 75,000-100,000/ $\mu$ L	Platelet count 75,000- <u>99,999</u> / $\mu$ L Second occurrence of platelet count 75,000- <u>99,999</u> / $\mu$ L	Revised to account for numerical overlap
- Restrictions During Study, #5	Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours of receiving study drug.	Subjects are not permitted to take proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to receiving study drug <u>and/or within 6 hours after receiving</u> study drug.	Revised for consistency and precision
- Demographics and Baseline Characteristics	• Race ( <del>white, American Indian/Alaska native, Asian, native Hawaiian or other Pacific Islander, black/African American</del> )	• Race ( <u>Asian, Black, Caucasian, Other, Unknown</u> )	Language revised for more inclusive race descriptors
- Subject Withdrawal Criteria	N/A	If a subject is lost to follow-up or withdraws from study treatment, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.	Additional information added to define sufficient attempts at follow-up.
- Study Drug Storage	The 100-mg capsules (unlabeled active pharmaceutical ingredient) will be stored at 2°C to 30°C.	The 100-mg capsules (unlabeled active pharmaceutical ingredient) will	Storage conditions revised per current product storage conditions.

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
		be stored at <u>15°C</u> to <u>25°C</u> .	
- Study Drug Administration	N/A	<u>Water is permissible during the fasting period; if necessary, a light snack (per physician approval) may be given 4 hours prior to oral administration.</u>	Addition made to account for operational flexibility given the long fasting period required of subjects
- Section 12.2 Adverse and Serious Adverse Events	<i>See below for original text</i>	<i>See below for revised text</i>	Updated for consistency with other recent niraparib protocols.
<b>(ORIGINAL TEXT) Section 12.2 Adverse and Serious Adverse Events</b>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
<b>1.1. Adverse and Serious Adverse Events</b>			
<b>1.1.1. Definition of Adverse Events</b>			
<b>1.1.1.1. Adverse Event</b>			
<p>An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p> <p>All AEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by TESARO.</p> <p>Adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (version 16.1).</p>			
<b>1.1.1.2. Serious Adverse Event</b>			
<p>A serious adverse event (SAE) is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow up) and at any dose of the investigational product that fulfills one or more of the following:</p> <ul style="list-style-type: none"><li>• Results in death</li><li>• Is immediately life threatening</li><li>• Requires in-patient hospitalization or prolongation of existing hospitalization</li><li>• Results in persistent or significant disability or incapacity</li><li>• Results in a congenital abnormality or birth defect</li><li>• It is an important medical event that may jeopardize the subject and may require medical or surgical intervention or treatment to prevent 1 of the outcomes listed above.</li></ul> <p>Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc) will not be considered an</p>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline&gt;</u> )	Rationale
<del>SAE; however, any AE that prolongs hospitalization will be considered an SAE.</del>			
<del>All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by TESARO.</del>			
<b>1.1.1.3. Suspected Unexpected Serious Adverse Reaction</b>			
<del>Any AE that is serious, associated with the use of study drug, and unexpected (defined as not listed in the appropriate section of the current Investigator's Brochure [TESARO 2014]) is referred to as a suspected unexpected serious adverse reaction (SUSAR) and requires the following additional reporting requirements:</del>			
<ul style="list-style-type: none"> <li>• If the SUSAR is fatal or life threatening, associated with the use of study drug, and unexpected, regulatory authorities, Institutional Review Boards (IRBs), and Independent Ethics Committees (IECs) will be notified within 7 calendar days after the Sponsor or designee learns of the event. Additional follow up information (cause of death, autopsy report, and hospital report) should be reported within an additional 8 calendar days (15 days total).</li> <li>• If the SUSAR is not fatal or life threatening but is otherwise serious, associated with the use of study drug, and unexpected, regulatory authorities, IRBs, and IECs will be notified within 15 calendar days after the Sponsor or designee learns of the event.</li> </ul>			
<del>The Sponsor or designee will notify the investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of subjects. Follow up information may be submitted, if necessary.</del>			
<del>The Sponsor or designee will also provide annual safety updates to the regulatory authorities, IRBs, and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.</del>			
<b>1.2. Relationship to Study Drug</b>			
<del>The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:</del>			
<ul style="list-style-type: none"> <li>• <u>Related</u>: A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.</li> <li>• <u>Likely related</u>: A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to</li> </ul>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<p>treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.</p> <ul style="list-style-type: none"> <li>• <u>Unlikely to be related:</u> A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.</li> <li>• <u>Unrelated:</u> A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.</li> </ul>			
<p>The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause and effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”</p>			

### 1.3. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center. Clinically significant changes in laboratory values, blood pressure, and pulse rate need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from signing of the consent form until the end of the study. Serious AE information will be collected from signing of the consent form until 30 days following the last dose of study drug. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Investigators should assess the severity of AEs according to CTCAE ([HHS 2009](#)).

In general, CTCAE version 4.02 severity grades are the following:

- Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3: Severe or medically significant but not immediately life threatening, hospitalization or prolongation of

Section(s)	Previous Text (deleted text shown by strikethrough)	Revised and/or Updated text (added text shown by underline)	Rationale
	hospitalization indicated, disabling, or limiting self care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).		
	<ul style="list-style-type: none"> <li>• Grade 4: Life threatening consequences or urgent intervention indicated.</li> <li>• Grade 5: Death related to AE.</li> </ul>		
	It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under <a href="#">Section 1.1.1.2</a> . An AE of severe intensity may not be considered serious.		
	The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report form and reported to the PPD Pharmacovigilance Department staff at the SAE Hotline number at any time.		
	Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.		
	The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.		
	Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.		
<b>1.4. Reporting Adverse Events</b>			
	All SAEs (related and unrelated) will be recorded from the signing of the consent form until 30 days following the end of treatment exposure. Planned hospitalization will not be considered an SAE ( <a href="#">Section 1.1.1.2</a> ). Any SAEs considered related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to PPD within 1 business day of the first awareness of the event. The Investigator must complete, sign, and date the SAE pages; verify the accuracy of the information recorded on the SAE pages with the corresponding source documents; and send a copy by fax to the PPD Pharmacovigilance Department staff. The Investigator and staff are encouraged to contact the Medical Monitor and the PPD Pharmacovigilance Department staff at the SAE Hotline number at any time.		
	Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the subject's personal identifiers removed. All relevant information		

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<p>obtained by the Investigator through review of these documents will be recorded and faxed within 24 hours of receipt of the information. If a new SAE report form is faxed, then the Investigator must sign and date the form.</p> <p>The minimum information required for an initial report includes the following:</p> <ul style="list-style-type: none"><li>• Name of person sending the report (ie, name and address of Investigator)</li><li>• Patient identification (screening/randomization number, initials, and NOT the subject's name)</li><li>• Protocol number</li><li>• Description of SAE</li><li>• Causality assessment, if possible</li></ul> <p>However, as many points as possible on the SAE report form should be covered in the initial report, or the completed SAE report form itself must be faxed to the PPD Pharmacovigilance Department staff. In addition, the event must be documented in the eCRF.</p> <p>After receipt of the initial report, the safety center will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event.</p> <p>The Investigator and the Sponsor (or the Sponsor's designee) will review each SAE report, and the Sponsor or the Sponsor's designee will evaluate the seriousness and the causal relationship of the event to study drug. In addition, the Sponsor (or the Sponsor's designee) will evaluate the expectedness according to the Investigator's Brochure (<a href="#">TESARO 2014</a>). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.</p> <p>Additional follow up information, if required or available, should be faxed within 1 business day of receipt, and this follow up information should be completed on a follow up SAE form, placed with the original SAE information, and kept with the appropriate section of the eCRF and/or study file.</p> <p>TESARO is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB or IEC of all SAEs that occur at his or her study center.</p>			
<p><b>(REVISED TEXT) Section 12.2 Adverse and Serious Adverse Events</b></p>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<b>1.1. Adverse and Serious Adverse Events</b>			
<b>1.1.1. <u>Definition of Adverse Events</u></b>			
<b>1.1.1.1. <u>Adverse Event</u></b>			
<p>An AE is any <u>untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.</u></p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p> <p>AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.</p> <p>Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.</p> <p>All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by subject), must be documented.</p> <p>A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study treatment has been administered.</p>			
<b>1.1.1.2. <u>Serious Adverse Event</u></b>			
<p>An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of the investigational product that fulfills one or more of the following:</p> <ul style="list-style-type: none"> <li>• <u>Results in death</u></li> <li>• <u>Is life-threatening</u> <ul style="list-style-type: none"> <li>– <u>This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe</u></li> </ul> </li> </ul>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<ul style="list-style-type: none"> <li>• <u>Requires inpatient hospitalization or prolongation of existing hospitalization</u></li> <li>• <u>Results in persistent or significant disability or incapacity</u></li> <li>• <u>Is a congenital anomaly or birth defect</u></li> <li>• <u>Is an important medical event(s)</u> <ul style="list-style-type: none"> <li>– <u>An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.</u></li> </ul> </li> </ul>			

Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

A distinction should be drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

**1.1.1.3. Submission of Expedited Reports to Regulatory Authority, Sites, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

Per regulatory requirements, if an SAE report is required to be submitted to a Regulatory Authority a copy of this report (Council for International Organizations of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigators/site. TESARO or its designee will submit a copy of the report to their respective IRB or IEC.

**1.2. Relationship to Study Drug**

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

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<ul style="list-style-type: none"> <li>• <u>Related:</u> A clinical event, including a laboratory test abnormality, with a plausible temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the treatment should be clinically plausible.</li> <li>• <u>Likely related:</u> A clinical event, including a laboratory test abnormality, with a reasonable temporal relationship to treatment administration that cannot be explained by concurrent disease or other drugs or chemicals.</li> <li>• <u>Unlikely to be related:</u> A clinical event, including a laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and a concurrent disease or other drugs or chemicals provide likely explanation.</li> <li>• <u>Unrelated:</u> A clinical event, including a laboratory test abnormality, with little or no temporal relationship to treatment administration that is typically explained by concurrent disease or other drugs or chemicals.</li> </ul>			

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

**1.3. Recording Adverse Events**

AEs and SAEs will be collected from the time of signing the ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see [Error! Reference source not found.](#), [Error! Reference source not found.](#), and [Error! Reference source not found.](#) for schedules of events). All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the study center.

Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the above SAE reporting process.

Abnormal laboratory values that constitute an AE or SAE must be collected. Investigators should assess the severity of AEs according

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<p>to CTCAE (<a href="#">HHS 2009</a>).</p>			
<p>In general, CTCAE version 4.02 severity grades are the following:</p>			
<ul style="list-style-type: none"><li>• Grade 1: Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.</li><li>• Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).</li><li>• Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, or limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).</li><li>• Grade 4: Life-threatening consequences or urgent intervention indicated.</li><li>• Grade 5: Death related to AE.</li></ul>			
<p>It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under <a href="#">Section 1.1.1.2</a>. An AE of severe intensity may not be considered serious.</p>			
<h4>1.4. Reports of Pregnancy</h4> <p>The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. Should a pregnancy occur, it must be recorded on the pregnancy report notification form and reported to the Sponsor.</p> <p>Pregnancies occurring in subjects enrolled in a study or in a female partner of a male subject must be reported and followed to outcome. The Investigator is responsible for documenting the course and outcome of any pregnancy that occurs while a subject is enrolled in the study and any pregnancy that occurs within 90 days after a subject's last dose.</p> <p>Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.</p> <p>Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance</p>			

Section(s)	Previous Text (deleted text shown by <del>strikethrough</del> )	Revised and/or Updated text (added text shown by <u>underline</u> )	Rationale
<p>with the procedure for reporting SAEs (see <a href="#">Section 1.5</a>).</p>			
<p>The investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.</p>			
<p>The Investigator should follow-up with the subject or the subject's female partner until delivery or termination of pregnancy even if the subject was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.</p>			
<p>In the event the pregnancy outcome occurs after the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor, or designee, within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs.</p>			
<p><b>PREGNANCY CONTACT INFORMATION</b></p>			
<p>Email: <u>PI</u> [REDACTED]</p>			
<p>Fax: <u>PI</u> [REDACTED]</p>			
<p>Telephone: <u>PI</u> [REDACTED]</p>			
<p><b>1.5. Reporting Adverse Events</b></p>			
<p>The Investigator must report any SAE once he/she becomes aware of within 24 hours of becoming aware of the event. SAEs must be reported using the following contact information:</p>			
<p><b>SAE REPORTING CONTACT INFORMATION</b></p>			
<p>Email: <u>PI</u> [REDACTED]</p>			
<p>Fax: <u>PI</u> [REDACTED]</p>			
<p>Telephone: <u>PI</u> [REDACTED]</p>			
<p>For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report Form must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the</p>			

<b>Section(s)</b>	<b>Previous Text</b> (deleted text shown by <u>strikethrough</u> )	<b>Revised and/or Updated text</b> (added text shown by <u>underline</u> )	<b>Rationale</b>
<u>follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.</u>			
<u>Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the subject's personal identifiers (eg, subject name, medical record number) removed according to local regulations. The Investigator must sign and date all SAE forms.</u>			
<u>The minimum information required for an initial SAE report is:</u>			
	<ul style="list-style-type: none"> <li>• <u>Name of person sending the report (ie, name, address of Investigator)</u></li> <li>• <u>Subject identification (screening/randomization number, initials, NOT subject name)</u></li> <li>• <u>Protocol number</u></li> <li>• <u>Description of SAE</u></li> <li>• <u>Causality assessment</u></li> </ul>		
<u>In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual business hours, Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).</u>			
<u>After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information</u>			
General	PPD Pharmacovigilance Department	DSA	Vendor for reporting serious adverse events has changed.



## Note to File

**Protocol Number:** PR-30-5015-C

**Study Title:** Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

**Subject:** Version 2.0 vs Version 2.1

**Date:** 22-Jan-2015

This Note to File documents that Protocol Amendment# 1 version 2.0 dated 01-Dec-14 was submitted to PPD for review but was not submitted to the Ethics Committee because an error in the protocol was identified prior to the submission. Tesaro revised the protocol and submitted Protocol Amendment# 1 version 2.1 dated 04-Dec-14 to PPD, who submitted it to the Ethics Committee for review and approval.

In summary, only the following protocols were submitted and approved by the Ethics Committee and Board of Directors:

- Original Protocol version 1.0 dated 28-May-14
- Protocol Amendment# 1 version 2.1 dated 04-Dec-14

<b>Name:</b> PI [REDACTED]	<b>Signature:</b> PI [REDACTED]
<b>Title:</b> Senior Manager, Medical Writing	D [REDACTED] 22 Jan 2015



## Note to File

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<b>Title:</b> Senior Manager, Medical Writing	D [REDACTED] 22 Jan 2015



# FORM

TITLE: <b>Note to File</b>	FORM NO.: <b>1040-00023-QA</b>	REV.: <b>00</b>	PAGE: <b>1 of 3</b>
	AUTHOR: <b>PI</b>	GOVERNING DOCUMENT NO.: <b>1000-00009-QA</b>	

From: PI

Date: 26 Oct 2015

Subject: PR-30-5015 v.4.1 inconsistency

Protocol Number: PR-30-5015 v.4.1

Protocol Title: Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

During the review of PR-30-5015-C Amendment 3 (11 September 2015, version 4.1), the following inconsistency was noted:

- Footnotes of *Table 2, Schedule of Assessments: Part 2* and footnote n of *Table 3, Schedule of Assessments: Open-Label Extension Study* both state, “FISH, MDS test result must be negative for cytogenetic abnormalities commonly observed in myeloid malignancies. The FISH, MDS result must be received prior to randomization.”
- *Section 8.1.11 Blood and Tissue Samples* states, “Whole blood samples will be collected for all subjects during screening and at EOT. Some samples will be used to determine eligibility per MDS/AML-related criteria (see Section 4). These test results must be received prior to randomization.”

PR-30-5015-C, however, is not a randomized study. *Section 5.4 Randomization and Blinding* states, “Subjects will not be randomly assigned and instead may choose in which part of the study to participate (Section 3.3). This is an unblinded study.” The references to randomization outlined above are artifacts of a program-wide safety amendment, and should state that results must be received prior to first dose of study drug.

As study PR-30-5015-C is well-established as a non-randomized study, there is no concern of safety or procedural aberrations that could result from this discrepancy. This letter serves to clarify the aforementioned inconsistency.



# FORM

TITLE:

**Note to File**FORM NO.:  
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PAGE:  
2 of 3AUTHOR:  
PIGOVERNING DOCUMENT NO.:  
1000-00009-QA

Sign: PI

Date: 28 Oct 2015

Printed Name:  
PI

Title: SR. MEDICAL WRITER

Reviewed and Approved:

Date:

Printed Name:

Title:

Reviewed and Approved:	Printed Name:
Date:	Title:



# FORM

TITLE:

**Note to File**FORM NO.:  
1040-00023-QAREV.:  
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PAGE:  
3 of 3AUTHOR:  
PIGOVERNING DOCUMENT NO.:  
1000-00009-QA**REVISION HISTORY:**

Rev Number	Change	Justification
00	New	



## FORM

TITLE: <b>Note to File</b>	FORM NO.: 1040-00023-QA	REV.: 00	PAGE: 1 of 2
	AUTHOR: PI	GOVERN NG DOCUMENT NO.: 1000-00009-QA	

From: PI Senior Director Clinical Pharmacology and Drug Disposition

Date: 9-March-2016

Subject: Documentation of deviations from urine and fecal sample collection stop criteria in Part 2

Protocol Number: PR-30-5015-C

Protocol Title: Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib in Subjects with Cancer

A revision to the urine and fecal collection stop criteria, for patients PI enrolled in Part 2 of the protocol was proposed by the site to TESARO, based on the site's experience with the first patient to whom these criteria applied PI. In consultation with the site, TESARO agreed to amend the urine and fecal collection stop criteria to be included in Amendment 3 of Protocol Version 4.1. The revised stop criteria would maintain the scientific integrity of the study with a reduced burden for the patients.

During the interim time between the agreement of the proposed changes and prior to Ethics Committee approval of Protocol Version 4.1 incorporating these changes, the site instituted the revised excreta stop criteria, in agreement with TESARO. These departures from the protocol were tracked as deviations, and are noted below:

Pt # PI	No urine or fecal collection after Day 14
Pt #	No urine collection after Day 10; no fecal collection after Day 9
Pt #	No fecal collection after Day 14
Pt #	No urine collection after Day 17; No fecal collection after Day 16
Pt #	No urine or fecal collection after Day 11

Signature: PI	Printed Name: PI
Date:	Title: Assoc. Director, Clinical Operations

Reviewed and Approved: PI	Printed Name: PI
Date:	Title: Sr. Dir. Clinical Pharmacology



## FORM

TITLE: <b>Note to File</b>	FORM NO.: 1040-00023-QA	REV.: 00	PAGE: 2 of 2
	AUTHOR: PI	GOVERN NG DOCUMENT NO.: 1000-00009-QA	

### REVISION HISTORY:

Rev Number	Change	Justification
00	New	