

## 16.1.9 DOCUMENTATION OF STATISTICAL METHODS

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NA=not applicable.

**TESARO, Inc.**

**PR-30-5015-C**

**ABSORPTION, METABOLISM, EXCRETION, AND THE  
DETERMINATION OF ABSOLUTE BIOAVAILABILITY OF NIRAPARIB  
IN SUBJECTS WITH CANCER**

**February 01, 2016**

**Statistical Analysis Plan**

**Final Version 1.0**

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan based on protocol amendment 2 version 3. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

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## List of Abbreviations

Abbreviation or Special Term	Explanation
$\infty$	Infinity
%AUC <sub>exp</sub>	Percentage of AUC extrapolated between AUC <sub>0-t</sub> and AUC <sub>0-inf</sub> . For profiles where %AUC <sub>exp</sub> > 30%, AUC <sub>0-inf</sub> will be listed but excluded from summary statistics.
%CV	Percent coefficient of variance
AE(s)	Adverse event (or events)
Aef <sub>t1-t2</sub>	Amount of drug excreted into the feces for each collection interval (t1-t2)
Aef <sub>total</sub>	Amount of drug excreted into the feces over the entire collection interval
Ae <sub>total</sub>	Total amount of drug excreted into the urine and feces combined over the entire collection interval
Aeu <sub>t1-t2</sub>	Amount of drug excreted into the urine for each collection interval (t1-t2)
Aeu <sub>total</sub>	Amount of drug excreted into the urine over the entire collection interval
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration versus time curve
BLQ	Below lower limit of quantification
BUN	Blood urea nitrogen
CBC	Complete blood count
CL <sub>r</sub>	Renal clearance

Abbreviation or Special Term	Explanation
CL/F	Apparent oral clearance
C <sub>max</sub>	Maximum observed plasma concentration.
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG(s)	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
F	Absolute bioavailability
Fef <sub>t1-t2</sub>	Fraction of systemically available drug excreted into the feces for each collection interval (t1-t2)
Fef <sub>total</sub>	Fraction of systemically available drug excreted into the feces over the entire collection interval
Fe <sub>total</sub>	Total fraction of systemically available drug excreted into the urine and feces combined over the entire collection interval
Feu <sub>t1-t2</sub>	Fraction of systemically available drug excreted into the urine for each collection interval (t1-t2)
Feu <sub>total</sub>	Fraction of systemically available drug excreted into the urine over the entire collection interval
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase

Abbreviation or Special Term	Explanation
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
INR	International normalized ratio
IV	Intravenous(ly)
$K_{el}$	Terminal elimination rate constant
LDH	Lactate dehydrogenase
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NCI	National Cancer Institute
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT(s)	Preferred term(s)
QD	Once a day
QTc	Corrected QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
StD	Standard deviation
SOC	System Organ Class
$T_{max}$	Maximum observed plasma concentration
TEAE	Treatment-emergent Adverse Event
$t_{1/2}$	Terminal phase half-life

Abbreviation or Special Term	Explanation
Vd/F	Apparent oral volume of distribution
WBC	White blood cells
WHO	World Health Organization

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## 1. Introduction

This is a Phase I, open-label trial 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). This statistical analysis plan (SAP) will cover both safety and pharmacokinetics (PK) in the Main study, Part 1 and Part 2, and safety assessments in the Extension study, based on clinical study protocol PR-30-5015-C (Amendment 3).

## 2. Objectives

### 2.1. Primary Objective

- 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) combined with a 300 mg oral dose of 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 and Plan

This is an open-label study with 2 parts and an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in compliance with 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 × 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 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.

1. **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.
2. If the total radioactivity in the Day 14 fecal or urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity  $\leq 85\%$  (feces and urine), then fecal or urine samples will be collected every 24 hours through Day 21.
3. If the total radioactivity in the Day 21 fecal or urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity  $\leq 85\%$  (feces and urine), then fecal or urine samples will continue to be collected every 24 hours.
4. Fecal or urine sample collection will stop at the end of Day 21 if the recovered radioactivity is below 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 radioactivity is below 1% (per 24 hours) for two consecutive days after Day 21.

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 1. The Screening visit for the Extension study 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 Part 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 (Protocol 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 (Protocol Section 8.4), or until the subject can be transitioned to the rollover 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.

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

The schedule of assessments for Part 1, Part 2, and the Extension study are presented in Appendix C.

### 3.2. Treatments

At the Screening visit, subjects will be offered the option to participate in either Part 1 or Part 2 until either 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.

### 3.3. Dose Adjustment/Modifications

Dose adjustment / modifications will be applied only to the Extension study.

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 adverse event (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 1 if prophylaxis is not considered feasible. Upon rechallenge, 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 per patient will be permitted throughout the study (including the Extension study).

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 or below 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 1: 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 ≥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 2.

**Table 2: Niraparib Dose Modification/Reduction for Hematologic Toxicities**

Event <sup>a</sup>	Dose <sup>b</sup>
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.
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 patients with a platelet count  $\leq 10,000/\mu$ L, a prophylactic platelet transfusion per clinical guidelines of the American Society of Clinical Oncology Group 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 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).

#### **4. General Statistical Considerations**

Analyses will be primarily descriptive in nature. No formal statistical tests will be performed. Summary tabulations will be presented that display the number of observations, mean, standard deviation (StD), median, minimum, and maximum for continuous variables, and the number and percent (calculated using non-missing values) per category for categorical data, unless specified otherwise. All data will be listed in data listings.

Baseline is generally defined as the latest no-missing value or evaluation prior to the first study drug administration.

Final analysis for the study and clinical study report (CSR) will be performed after Part 1 and Part 2 of the study are completed. An addendum to the CSR will be generated once the safety information from the Extension study is completed.

##### **4.1. 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 in each Part and accounts for interindividual variability. Enrollment may be extended to replace subjects discontinued during the study.

##### **4.2. Randomization, Stratification, and Blinding**

Subjects will not be randomly assigned, and instead will choose the part (either Part 1 or Part 2) of the study in which they will participate. As stated previously, when either Part of the study is fully enrolled, subjects will only be allowed to participate in the remaining Part. This is an open-label and unblinded study.

### 4.3. Analysis Populations

The following sections describe the analysis populations that will be used in the statistical analyses.

#### 4.3.1. All-Enrolled Population

The all-enrolled population will consist of all subjects enrolled in the study. Listings will include data collected from all enrolled subjects.

#### 4.3.2. Safety Population

The safety population will consist of all participants who received at least 1 partial or complete dose of study drug. The safety population will be used for all safety listings and tables.

#### 4.3.3. PK Population

The PK population will consist of all subjects who received study drug and provided adequate PK samples to calculate PK parameters.

## 5. Subject Disposition

### 5.1. 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 (eg, lost to follow-up, AE). In addition, the number of subjects in each analysis population will be summarized by group. A listing will present data for subject disposition.

### 5.2. Protocol Deviations and Inclusion / Exclusion Criteria

The Sponsor will provide protocol deviations in an Excel file format, and protocol deviations will be mapped into the analysis dataset. A summary of significant protocol deviations by type will be produced and a listing of protocol deviations will be provided based on the all-enrolled analysis populations.

All inclusion and exclusion information (inclusion and exclusion criteria are detailed in Sections 8.1 and 8.2 of the protocol) on enrolled subjects will be included in a by-subject listing. The listing will include whether all criteria were satisfied. For subjects who did not satisfy the criteria, the criteria number will be listed with the deviation.

## 6. Demographics and Baseline Characteristics

Demographics and baseline information will be summarized descriptively by group for the safety population, PK population, and all-enrolled population. The demographic characteristics are age, sex, female of childbearing potential, race, and ethnicity. The baseline characteristics consist of history of drug, alcohol, or other substance abuse; smoking history; and Fluorescence In Situ Hybridization (FISH) test result.

A subject's age will be calculated using the date of the informed consent and date of birth: (date of informed consent – date of birth)/365.25 (years). Age will be summarized using descriptive statistics. The number and percentage of subjects by sex (male, female), race (Caucasian, Black,

Asian, Unknown, and Other), and ethnicity (Hispanic or Latino, Not Hispanic or Latino), will also be reported. Percentages will be based on the total number of subjects in the relevant population.

All data in subject demographic and baseline characteristics will be listed in data listings.

### **6.1. Medical 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 computed tomography (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, 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

Medical history and history of prior therapies will be presented in data listings. These listings will present all subjects in the safety population.

## **7. Treatments and Medications**

### **7.1. Prior and Concomitant Medications**

A medication will be categorized as prior medication if the medication end date falls before the first dose date. A medication will be categorized as concomitant if the medication end date falls after the first dose date or is ongoing at study completion. In addition, any medications taken on first dose date will be categorized as concomitant.

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

All medications will be mapped to generic terms according to the World Health Organization (WHO) drug dictionary, version SEP 2015. Subjects in the safety population who had prior medication and/or are taking concomitant medications will be summarized descriptively by group. Summarization will be done by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug preferred term. At each level of summarization, a

subject is counted once if he/she reported one or more medications in that ATC classification and WHO drug preferred term.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as detailed in Appendix A.

Prior and concomitant medications will be presented in a by-subject listing. The listing will include drug class, preferred term, the start date, stop date, dosage, frequency, indication, and route of administration of prior and concomitant medications.

Concomitant procedures, as collected in CRF, will also be presented in data listings.

## 7.2. Study Treatments

All dosing information will be presented in separate listings for Part1 (IV and oral), Part 2, and Extension.

Exposure to study drug during the Extension study will include the number of cycles, duration, and amount of study drug taken during the study.

- Number of cycles started 1, 2 ...
- Total duration calculated as (last dose date - first dose date +1).
- Dose intensity (mg/day) will be derived as sum of the daily doses actually consumed divided by total duration.

Total duration and dose intensity will be summarized using descriptive statistics. The number of cycles started will be summarized by the numbers and percentages of subjects with study medication records for the given cycle. The numbers and percentages of subjects with any dose reduction and any dose interruption (including missed doses) will be presented. An additional summary will present dose reductions and interruptions due to AEs.

## 8. Efficacy Analysis

There is no planned efficacy analysis.

## 9. Safety Analysis

The safety population will be used to summarize the safety of niraparib. Safety will be evaluated by incidence, severity, and duration of any adverse reactions and clinically significant changes or abnormalities in the subject's physical examinations, vital sign measurements, laboratory test results, and electrocardiogram (ECG) findings.

TESARO will monitor safety throughout the trial via the following:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of non-serious AEs as they are recorded in the eCRF

Findings discovered to have immediate implications for the management of trial subjects will be communicated to the Principal Investigator (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 sign measurements, AE reporting, and ECG monitoring.

### 9.1. Adverse Events

Adverse event terms recorded by the clinical site will be mapped to preferred terms, using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. AEs that occur after any subject has been enrolled, before treatment, or during treatment, whether or not they are related to the study drug, will be recorded on the eCRF.

An AE is defined as 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. A treatment-emergent AE (TEAE) is defined as an AE that begins or that worsens in severity after at least 1 dose of study drug has been administered.

A related AE is determined by the investigator, depending on, in his or her medical judgment, whether 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." For summaries by relationship, AEs with missing relationship are counted as "related." For summaries by CTCAE grade, AEs with missing CTCAE grade are counted as CTCAE grade 3 – Severe. If the AE start or end date is missing, the missing date will be imputed as shown in Appendix A.

The number and percentage of subjects experiencing an AE will be summarized for each system organ class (SOC) and preferred term by group. The incidence of AEs table will include only 1 occurrence of any given preferred term per subject in counting the number of subjects with the preferred term. If a subject reports the same preferred term multiple times, that preferred term will only be counted once per subject. As with the preferred term, if a subject reports multiple AEs within the same SOC, then that SOC will only be counted once per subject. Percentages will be calculated using the total number of subjects in the safety population as the denominator.

All AEs will be presented in a listing.

#### 9.1.1. Relationship of Adverse Events to Study Drug

Adverse events by relationship to the study drug will be summarized by incidence of occurrence for each SOC and preferred term, by group. The possible relationships are "related," "likely related," "unlikely related," and "unrelated." In the AE relationship table, if a subject reports multiple occurrences of the same AE, only the most closely related occurrence will be presented. A summary of related AEs (likely related, related) will also be presented in a table by incidence of occurrence. Percentages will be calculated using the number of subjects in the safety population. Adverse events that are missing a relationship will be presented in the summary table as "related," but will be presented in the data listing with a missing relationship.

#### 9.1.2. Severity of Adverse Event

A summary of AEs by severity (CTCAE grade) will be presented in a table. The severity presented will represent the most extreme severity captured in the data. If a subject reported

multiple occurrences of the same AE, only the most severe occurrence will be presented in the table. Percentages will be calculated using the number of subjects in the safety analysis population. In addition, a summary of severe AEs (CTCAE Grade 3 or higher) will be provided. Adverse events that are missing a CTCAE grade will be presented in the summary table as CTCAE grade 3 (Severe) but will be presented in the data listing with a missing severity.

#### **9.1.3. Serious Adverse Events**

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or followup) 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) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE.

Subjects experiencing at least 1 SAE will be summarized by SOC and preferred term. A by-subject listing will present only SAEs with SOC, preferred term, reported term, start date, stop date, duration (Days), outcome, grade, action taken and relationship to the treatment.

#### **9.1.4. Adverse Events Leading to Study Discontinuation**

Subjects experiencing at least 1 AE resulting in discontinuation from the study will be presented in a listing.

#### **9.1.5. Death**

A by-subject listing of the deaths will be presented. All deaths occurring throughout the study, from the time ICF is signed until the followup or early termination visit will be included.

### **9.2. Clinical Laboratory Evaluations**

#### **• Parts 1 and 2**

Hematology assessments include the following: hemoglobin, platelets, white blood cells (WBC), differential white cell count.

Coagulation assessments include activated partial thromboplastin time (aPTT) and international normalized ratio (INR).

Blood chemistry assessments include the following: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), total protein, albumin, lactate dehydrogenase (LDH), and amylase.

- **Extension Study**

All hematology and blood chemistry results will be presented in data listings. Observed values at baseline and changes from baseline will be summarized descriptively by study group (ie, Part 1 subjects, Part 2 subjects, and Extension study subjects) and by study visit. Individual by-subject data listings will be presented. Individual by-subject data listings of clinically significant results will also be presented. Shift tables of baseline versus post-baseline, based on normal ranges, will also be presented for select chemistry and hematology laboratory parameters.

### **9.3. Vital Sign Measurements**

Vital sign measurements include systolic blood pressure, diastolic blood pressure, body temperature, heart rate, weight, and height. Observed values at baseline and changes from baseline will be summarized descriptively by group (Part 1, Part 2, and Extension study) and by study visit for the safety population. Individual by-subject data listings of vital signs will be presented.

### **9.4. Physical Examination**

The number and percentage of subjects with an abnormal physical examination finding will be presented for each of the CRF-defined body systems. The summary will be presented by study group and by study visit. Individual by-subject data listings of physical examination findings will be presented.

### **9.5. Electrocardiograms**

The Screening ECG obtained before dosing will be used as the baseline for comparison of postbaseline values. Actual ECG values at baseline and changes from baseline will be summarized descriptively by study group and study visit, including PR interval and QTc. Individual by-subject data listings of ECG findings will be presented, with flags attached to QTc values of clinical significance.

### **9.6. Pregnancy Test**

Pregnancy test results for female subjects will be displayed in a listing.

### **9.7. Other Safety Data**

Individual data listings of ECOG performance status, confirmation diagnosis by CT scan; and test results for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) will be presented for each subject.

## 10. Pharmacokinetics

The PK analysis population will be used for PK analyses.

For the presentation of individual values and summary statistics, the following rules will be applied: number of subjects (N) will be reported as a whole number; for drug amount, drug concentrations, and concentration-dependent PK parameters, all summary statistics (mean, median, StD, minimum, and maximum) will have 3 significant digits, except for the percent coefficient of variation (%CV) and geometric mean, each of which will be presented to 1 decimal place. For time to maximum plasma concentration ( $T_{max}$ ), raw values (in hours), median, minimum, and maximum will be shown to 2 decimal places.

The following procedures will be used for plasma samples with concentrations that are below the lower limit of quantification (BLQ):

For calculation of PK parameters:

- Following the single dose administration, BLQ values at predose and up to the first quantifiable concentration should be replaced with zero.
- Following the first quantifiable concentration, BLQs between 2 quantifiable concentrations and BLQs at the terminal phase of the concentration-time profile should be set to "missing."
- Following the first quantifiable concentration, if a quantifiable concentration is followed by 2 consecutive BLQs in the terminal phase, all subsequent quantifiable concentrations should be assigned to "missing."

For calculated summary statistics of concentration data:

- Samples that are BLQ will be treated as zero in the calculation of summary statistics of concentrations at each scheduled time point.

### 10.1 Plasma and Whole Blood Concentrations

For Part 1, blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 minutes prior to dose), Day 1 (1 [ $\pm 2$  minutes], 1.5 [ $\pm 2$  minutes], 2 [within 1 minute prior to IV infusion], 2.125 [ $\pm 1$  minutes], 2.25 [within 1 minute post-infusion], 2.33 [ $\pm 1$  minutes], 2.66 [ $\pm 1$  minutes], 3 [ $\pm 2$  minutes], 4 [ $\pm 5$  minutes], 6 [ $\pm 5$  minutes], and 12 hours [ $\pm 15$  minutes] 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 minutes prior to dose), Day 1 (1 [ $\pm 2$  minutes], 1.5 [ $\pm 2$  minutes], 2 [ $\pm 2$  minutes], 3 [ $\pm 2$  minutes], 4 [ $\pm 5$  minutes], 6 [ $\pm 5$  minutes], and 12 hours [ $\pm 15$  minutes] 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 final PK draw should occur within  $\pm$  24 hours of the final urine or fecal sample.

For Part 2, blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 minutes prior to dose), Day 1 (1 [ $\pm$ 2 minutes], 2 [ $\pm$ 2 minutes], 3 [ $\pm$ 2 minutes], 6 [ $\pm$ 5 minutes], and 12 [ $\pm$ 15 minutes] 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).

### 10.2 Urine Concentrations

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. 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.

Urine concentrations of total radioactivity will be summarized by time interval using descriptive statistics; n, mean, geometric mean, median, StD, minimum, maximum, and %CV.

### 10.3 Fecal Concentrations

Fecal samples will be collected for Part 2 prior to study drug administration (0 hour), and all subsequent 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. 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.

Fecal concentrations of total radioactivity will be summarized by time interval using descriptive statistics; n, mean, geometric mean, median, StD, minimum, maximum, and %CV.

#### 10.4 Pharmacokinetic Parameters

The following PK parameters will be calculated for plasma total [ $^{14}\text{C}$ ]-radioactivity, [ $^{14}\text{C}$ ] niraparib and unlabeled niraparib for Part 1, and for plasma and whole blood total [ $^{14}\text{C}$ ]-radioactivity, for plasma unlabeled niraparib and M1 in Part 2, by noncompartmental method using WinNonlin Phoenix Version 6.2.1 or higher (Pharsight Corporation, St. Louis, Missouri); all calculations for final analysis will be based on actual sampling times:

Parameter	Definition
$C_{\max}$	Maximum observed plasma concentration.
$T_{\max}$	Time to reach maximum observed plasma concentration.
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity, calculated using the linear up/log down trapezoidal rule.
$AUC_{0-\text{last}}$	Area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration, calculated using the linear up/log down trapezoidal rule (the linear trapezoidal rule is applied up to the $T_{\max}$ and the log-linear trapezoidal rule is applied after the $T_{\max}$ )
	<ul style="list-style-type: none"> <li>• Linear trapezoidal rule:</li> </ul> $AUC_{t_1-t_2} = \frac{C_1 + C_2}{2} \times (t_2 - t_1)$ <ul style="list-style-type: none"> <li>• Log-linear trapezoidal rule:</li> </ul> $AUC_{t_1-t_2} = \sqrt{C_1 \times C_2} \times (t_2 - t_1)$
$t_{1/2}$	Terminal phase half-life, calculated as $t_{1/2} = \ln 2 / K_{el}$ .
$K_{el}$	Terminal elimination rate constant estimated from the linear regression of the natural log-transformed concentration over time at the terminal phase. In

order to estimate  $K_{el}$  during the terminal phase in the logarithmic concentration versus time curve after  $T_{max}$ , the points selected by WinNonlin will be confirmed or changed by visual inspection of the terminal phase of the logarithmic concentration-versus-time curve, if necessary. The linear regression method will be applied to at least 3 time points (excluding  $C_{max}$ ), including the last quantifiable time point. In the estimation of  $K_{el}$ ,  $R^2$  in general should be  $>0.80$  for the regression.

%AUC<sub>exp</sub>

Percentage of AUC extrapolated between AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>. For profiles where %AUC<sub>exp</sub>  $>30\%$ , AUC<sub>0-inf</sub> will be listed but excluded from summary statistics.

CL/F

Apparent oral clearance.

Vd/F

Apparent oral volume of distribution.

F

Absolute bioavailability of niraparib (Part 1 only), calculated as:

$$\frac{\frac{AUC_{0-inf} \text{ of niraparib from oral dose}}{300 \text{ mg}}}{\frac{AUC_{0-inf} \text{ of } [^{14}\text{C}]\text{-niraparib from IV dose}}{100 \mu\text{g}}} \times 100\%$$

All PK analyses will be conducted by the Department of Clinical Pharmacology, PPD Richmond, Virginia, USA.

The individual PK parameters will be presented in a data listing and summarized by group, analyte and matrix using descriptive statistics: n, mean, SD, %CV, median, minimum, and maximum. Geometric mean will also be included for all PK parameters except for  $T_{max}$ .

## 10.5 Urine and Fecal Pharmacokinetic Parameters (Part 2 Only)

The following urine and fecal PK parameters for total [ $^{14}\text{C}$ ]-radioactivity, urine parameters for unlabeled niraparib and M1 (Part 2 only) will be calculated. BLQ values will be treated as zero when calculating urine and fecal parameters.

Symbol	Definition
$A_{eu_{t1-t2}}$	Amount of drug excreted into the urine for each collection interval (t1-t2)
$A_{eu_{total}}$	Amount of drug excreted into the urine over the entire collection interval
$CL_r$	Renal clearance
$F_{eu_{t1-t2}}$	Fraction of systemically available drug excreted into the urine for each collection interval (t1-t2)
$F_{eu_{total}}$	Fraction of systemically available drug excreted into the urine over the entire collection interval
$A_{ef_{t1-t2}}$	Amount of drug excreted into the feces for each collection

	interval (t1-t2)
$A_{ef_{total}}$	Amount of drug excreted into the feces over the entire collection interval
$F_{ef_{t1-t2}}$	Fraction of systemically available drug excreted into the feces for each collection interval (t1-t2)
$F_{ef_{total}}$	Fraction of systemically available drug excreted into the feces over the entire collection interval
$A_{e_{total}}$	Total amount of drug excreted into the urine and feces combined over the entire collection interval
$F_{e_{total}}$	Total fraction of systemically available drug excreted into the urine and feces combined over the entire collection interval

### 11. Interim Analysis

No formal interim analysis is planned and an external Data Safety Monitoring Board will not be established for this study.

### 12. Changes in the Planned Analysis

No changes to the planned analyses are currently anticipated. However, due to the complexity and duration of the study, it is possible that emerging safety and/or efficacy signals may warrant additional exploratory analyses or amendment of the existing analyses. These will be explained in a supplement to this SAP, as the need arises.

## References

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Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program*. 2007:172-8.

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).

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## 13. Appendices

### 13.1. Appendix A: Imputation Algorithm for Partial and Missing Dates

#### Adverse Events

- If onset date is completely missing, then onset date is set to date of first dose.
- If (year is present and month and day are missing) or (year and day are present and month is missing):
  - If year = year of first dose, then set onset month and day to month and day of first dose
  - If year < year of first dose, then set onset month and day to 31 December.
  - If year > year of first dose, then set onset month and day to 01 January.
- If month and year are present and day is missing:
  - If year = year of first dose and
    - If month = month of first dose then set day to day of first dose date
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to 1<sup>st</sup> day of month
  - If year < year of first dose then set day to last day of month
  - If year > year of first dose then set day to 1<sup>st</sup> day of month
- For all other cases, set onset date to date of first dose

#### Concomitant Medications

- If start date is completely missing then start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing) then set start month and start day to 01 January.
- If start year and start month are present and start day is missing then set start day to 1<sup>st</sup> day of month.
- If end date is completely missing then end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing) then set end month and end day to 31 December.
- If end year and end month are present and end day is missing then set end day to last day of the month.

### 13.2. Appendix B: Adverse Event Severity Grades

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.

### 13.3. Appendix C: Schedule of Study Procedures

- 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	X	X	X	X	X	X	X	X
HBV/HCV/HIV screening <sup>d</sup>	X												
Clinical laboratory assessments <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												

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
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										
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													

- a. 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.
- b. Vital signs include blood pressure, pulse rate, and aural (tympanic) temperature. On Day 1, vital signs should be collected prior to study drug administration.
- c. If subject comes to the center and/or chooses to be admitted on Day -1.
- d. 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.
- e. 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.
- f. Must occur within 72 hours prior to dosing.
- g. Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.
- h. 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 protocol Section 12).
- i. Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.
- j. 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.
- k. 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.
- l. 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 minutes], 1.5 [±2 minutes], 2 [within 1 minutes prior to IV infusion], 2.125 [±1 minutes], 2.25 [within 1 minutes post-infusion], 2.33 [±1 minutes], 2.66 [±1 minutes], 3 [±2 minutes], 4 [±5 minutes], 6 [±5 minutes], and 12 hours [±15 minutes] 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).
- m. New serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit

• Schedule of Assessments: Part 2

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	1 5	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 <sup>d</sup>	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																	

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
Subject confinement		X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X						
[ <sup>14</sup> C]-niraparib administration <sup>k</sup>			X															
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
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.

- h. 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).
- i. Subjects will have a 12-lead ECG at the Screening Visit and on Day 1 (predose and 2 hours postdose) and Day 22.
- j. Subjects must provide the most recent CT scan (taken prior to enrollment) to confirm their cancer diagnosis.
- k. 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]), after an overnight fast of at least 10 hours. Subjects will continue fasting until 4 hours after administration of study drug.
- l. Blood samples for PK analysis will be collected at the following times: predose (0 hour, within 30 minutes prior to dose), Day 1 (1 [ $\pm 2$  minutes], 1.5 [ $\pm 2$  minutes], 2 [ $\pm 2$  minutes], 3 [ $\pm 2$  minutes], 4 [ $\pm 5$  minutes], 6 [ $\pm 5$  minutes], and 12 hours [ $\pm 15$  minutes] 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 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).
- m. Blood samples for metabolite profiling will be collected at the following times: predose (0 hour, within 30 minutes prior to dose), Day 1 (1 [ $\pm 2$  minutes], 2 [ $\pm 2$  minutes], 3 [ $\pm 2$  minutes], 6 [ $\pm 5$  minutes], and 12 [ $\pm 15$  minutes] 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).
5. 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 14 urine sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity  $\leq 85\%$  (feces and urine), then urine samples will be collected every 24 hours through Day 21. 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  $\leq 85\%$  (feces and urine), then urine samples will continue to be collected every 24 hours. Urine sample collection will stop at the end of Day 21 if the recovered radioactivity is below 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 radioactivity is below 1% (per 24 hours) for two consecutive days after Day 21.
- n.
- o. 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 14 fecal sample is detected to be higher than 0.1% and the total recovery of accumulative radioactivity  $\leq 85\%$  (feces and urine), then fecal samples will be collected every 24 hours through Day 21. 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  $\leq 85\%$  (feces and urine), then fecal samples will continue to be collected every 24 hours. Fecal sample collection will stop at the end of Day 21 if the recovered radioactivity is below 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 radioactivity is below 1% (per 24 hours) for two consecutive days after Day 21..
- p. New serious adverse events (SAEs; including deaths) will be collected for an additional 30 days after the treatment discontinuation visit

- 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	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
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.							

- <sup>a</sup> 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 2. 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 minutes predose and 2 hours  $\pm 15$  minutes postdose), Cycle 2/Day 1 Visit (within 30 minutes predose and 2 hours  $\pm 15$  minutes postdose), Cycle 4/Day 1 Visit (within 30 minutes predose), and Cycle 8/Day 1 Visit (within 30 minutes 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.

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