

[*] Prior Therapy; [*] Medical History*	-28 to -1	Demographics; Prior Anti-Cancer Therapies; Medical History- Prostate Cancer.
Eligibility criteria	-28 to -1	
Enrollment authorization form	-28 to -1	Complete, sign, and fax or email the form with requested items to sponsor or designee at least 2 business days before enrollment (day 1). Patient may proceed to day 1 when sponsor or designee approves by signed form or email correspondence.
12-Lead electrocardiogram	-28 to -1	Local.
Vital signs	-28 to -1	Measure blood pressure, heart rate, and temperature.
ECOG performance status	-28 to -1	Eastern Cooperative Oncology Group.
Physical examination, weight, height	-28 to -1	Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).
Pretreatment adverse events review	-28 to -1	Report serious and nonserious adverse event information from time of signed informed consent.
Prior and concomitant medications	-28 to -1	
Submit fresh or adequate archival tumor tissue. Alternatively, prior results from Foundation Medicine may be considered for eligibility with sponsor approval. If patient genetically qualifies based on prior tumor testing, submit adequate archival or fresh tissue if available.	Any time before -1 (Refer to Table 1)	If not obtained at the prescreening visit: submit tissue from a de novo biopsy of a safely accessible tumor lesion, or archival tumor tissue, for prospective central laboratory enrollment testing. Test results from prior tumor testing identifying DNA repair deficiencies likely to sensitize to PARP inhibition may be considered for eligibility. If sufficient residual DNA is available at Foundation Medicine this could be used to confirm a patient's eligibility for enrollment. Note that if eligibility for enrollment is established based on either prior results or residual DNA testing, available archival or de novo tumor tissue also should be submitted prior to Day 1, to support concordance analyses and additional molecular profiling, unless prohibited by local regulations or ethics committee (EC) decision. Note: biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel <u>may not be performed</u> for the sole purpose of determining study eligibility.
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Laboratory Evaluations		Refer to the central laboratory instruction manual for sample processing and for estimated turnaround time for results. All laboratory evaluations will be tested centrally except where noted.
Serum chemistry, hematology	-28 to -1	
Testosterone, PSA	-28 to -1	Up to 2 or 3 local prostate-specific antigen measurements (PSA) will be used to determine eligibility, including local PSA values that may have been obtained prior to the patient signing the study ICD and greater than 28 days before Day 1. PSA measurements must be consecutive and at least 1 week apart. The third PSA may, or may not, be the central lab screening PSA. If the screening central lab PSA is lower than local lab PSA #2, then a third local lab PSA may be submitted instead. A central PSA assessment will be done at screening for all patients. Screening PSA (as per central laboratory) must be ≥ 2 ng/mL for patients qualifying based only on PSA progression. Refer to Section 7.2.1 .
Radiographic Assessments		May use scans obtained as part of standard of care before consent was signed and within 42 days before day 1 if scans were performed per the specific study requirements (per imaging manual).
CT of chest; CT or MRI of abdomen and pelvis	-42 to -1	Computed tomography or magnetic resonance imaging.
Whole-body radionuclide bone scan	-42 to -1	

* Demographics, Prior Anti-Cancer Therapies and Medical History- Prostate Cancer will not be required for patients that have these data recorded at the prescreening visit.

Table 3. Study Schedule of Activities: Treatment*

Study Period or Visit	Treatment									Unsched ^[1]	Safety FU ^[2]
Study Week	1 ^{**}	3	5	7	9	13	17	21	25+ ^[3]	Varies	Varies
Window (Days) ^[4]	na	± 3 (± 7 for scans)								na	-3 to +10
Enrollment ID number	X										
General Activities											
Vital signs ^[5]	X	X	X	X	X	X	X	X	X	X	X
Physical exam, weight ^[6]	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X
BPI-SF, EQ-5D-5L ^[7]	X	X	X	X	X	X	X	X	X	X	X
Pain Log ^[19]		X	X	X	X	X	X	X	X	X	X
Analgesic Log ^[20]		X	X	X	X	X	X	X	X	X	X
Adverse events review ^[8]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensing ^[9]	X ^[7]		X		X	X	X	X	X	X (optional)	
Study drug accountability			X		X	X	X	X	X	X (optional)	
Central Lab Evaluations^[10]											
Serum chemistry, hematology ^{[3][11]}	X	X	X	X	X	X	X	X	X	X	X
Prostate-specific antigen ^[21]	X				X	X	X	X	X	X	X
Blood sample for PK ^[12]	X		X		X	X				X	

*

Study Period or Visit	Treatment									Unsched ^[1]	Safety FU ^[2]
	1 ^{**}	3	5	7	9	13	17	21	25+ ^[3]		
Study Week	na	± 3 (± 7 for scans)								Varies	Varies
Window (Days) ^[4]	na									na	-3 to +10
Blood sample for CTC enumeration ^[13]											
CC1											
Blood sample to be stored for reflex testing for viral hepatitis											
Contraception check ^[22]											
Radiographic Assessments ^[18]											
CT of chest, CT or MRI of abdomen and pelvis											
Bone scan											

*Patients enrolled as per prior versions of the protocol will follow the same schedule of activities and treatment/study discontinuation criteria.

**Includes Day 1, defined as the day subject receives his first dose of talazoparib.

1. Unscheduled visits/assessments can be done anytime necessary to assess or follow up adverse events, at the patient's request, or per investigator decision, or to account for any insufficient, inadequate, or missed sample or assessments. Perform imaging if disease progression is suspected. Data are to be entered in the appropriate CRF. If medically required, additional ECGs will be done with results entered in the CRF; clinically significant findings will be captured as adverse events.
2. Approximately 28 days after permanent treatment discontinuation of study drug or before initiation of a new antineoplastic or investigational therapy whichever occurs first. Phone patients for adverse event follow-up if they do not come to the clinic.
3. Visits repeat every 12 weeks while on study drug. Hematology and serum chemistry assessments will be completed every 8 weeks by the central laboratory while on study drug.
4. Drug supply must be taken into account when scheduling visits during windows. Visit procedures may be split across the window to allow for drug resupply and completion of study procedures.
5. Measure blood pressure, heart rate, and temperature.
6. Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms. Measure weight.

1. INTRODUCTION

1.1. Overview and Mechanism of Action

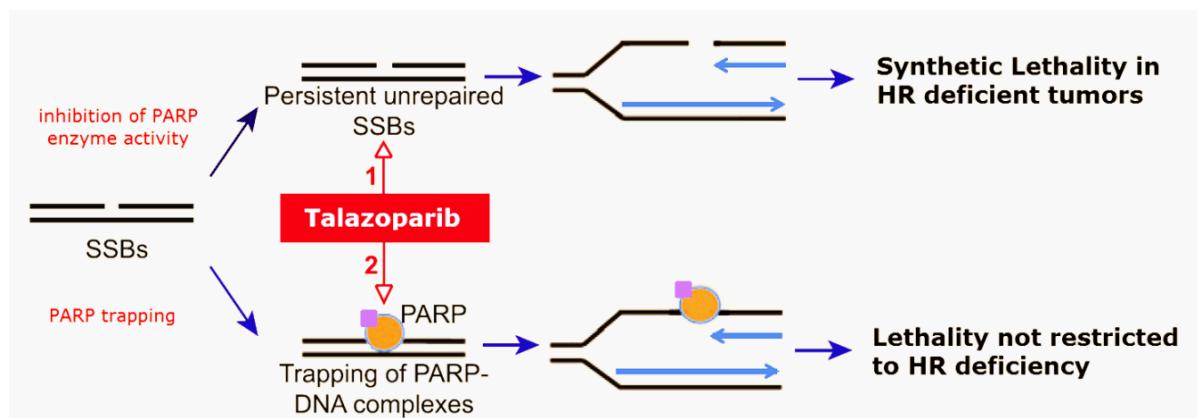
1.1.1. Overview

Talazoparib (also known as PF-06944076, MDV3800) is being investigated for the treatment of metastatic castration-resistant prostate cancer (mCRPC) with DNA damage repair deficiencies in men whose disease has previously progressed on novel hormonal therapy (NHT: enzalutamide and/or abiraterone acetate) given for the treatment of mCRPC and who were previously treated with taxane-based chemotherapy for metastatic disease.

1.1.2. Mechanism of Action/Indication

Talazoparib is a potent, orally bioavailable, small molecule poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor in development for the treatment of a variety of human cancers. PARP inhibitors including talazoparib exert cytotoxic effects via 2 mechanisms: (1) inhibition of PARP1 and PARP2 catalytic activity, and (2) PARP trapping, a process in which PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, thereby preventing DNA repair, replication, and transcription ([Murai et al, 2012](#)).

Figure 1. Dual Cytotoxic Mechanisms of PARP Inhibitors



Source: Adapted from Reference 1

PARP = poly (adenosine diphosphate-ribose) polymerase.

Inhibition of PARP catalytic activity (upper pathway) interferes with the repair of single-strand breaks, leading to replication fork damage that requires homologous recombination DNA repair for cell survival. Trapping of PARP–DNA complexes with PARP inhibitor (lower pathway; PARP inhibitor represented by ■) also leads to replication fork damage with more DNA repair processes required for cell survival.

Single-agent treatment with talazoparib has demonstrated potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA-damaging chemotherapy, including temozolomide and irinotecan, in both in vitro and in vivo preclinical models.

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Table 8. Talazoparib Dose Modifications Due to Adverse Events

Toxicity	Management of Adverse Events [1]
Nonhematologic laboratory grade ≥ 3 events, except abnormal liver tests ^[1]	<p>Hold talazoparib as follows:</p> <p>For clinically significant Grade 3 laboratory abnormalities hold talazoparib until the laboratory abnormality resolves to Grade ≤ 2 (to baseline grade for creatinine increases). Resume talazoparib at the same dose or reduce by 1 dose level per Figure 3.</p> <p>If Grade 3 laboratory abnormality recurs, hold talazoparib until the laboratory abnormality resolves to Grade ≤ 2 (to baseline grade for creatinine increases). Reduce talazoparib one dose level per Figure 3.</p> <p>For Grade 4 laboratory abnormalities, hold talazoparib. Resume talazoparib when the laboratory abnormality resolves to Grade ≤ 2 (to baseline grade for creatinine increases) at a 1 dose level reduction per Figure 3. Talazoparib must be discontinued if a Grade 4 adverse event recurs after treatment resumes. Implement supportive care per local guidelines. Contact sponsor to discuss potential dose modification.</p> <p>Talazoparib must be permanently discontinued for unresolved Grade 3 toxicity lasting longer than 14 days or for Grade 4 toxicity lasting longer than 3 days. Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the sponsor.</p>
Grade ≥ 3 abnormal liver tests	<p>Subjects who develop abnormal liver tests (AST, ALT, total bilirubin [TBili]), signs or symptoms consistent with hepatitis during study treatment may meet the criteria for temporarily withholding or permanently discontinuing study drug talazoparib.</p> <p>Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities if any of the following occur:</p> <ul style="list-style-type: none">• Subjects who develop AST or ALT $>5 \times$ ULN (without TBili $>2 \times$ ULN); OR• Subjects with baseline total bilirubin $<1.5 \times$ ULN who subsequently present with $>3 \times$ ULN; OR• Subjects with baseline total bilirubin $>1.5 \times$ ULN and $<3 \times$ ULN (eg, Gilberts) who subsequently present with bilirubin $>5 \times$ ULN. <p>If abnormalities resolve to baseline values within 2 weeks, there are no signs of drug induced liver injury (DILI), and none of the permanent discontinuation criteria are met, then upon discussion with the Sponsor, the investigator may re-challenge at a reduced dose level.</p> <p>Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities if any of the following occur:</p> <ul style="list-style-type: none">• Refer to Section 8.4.2 for potential DILI cases;• Subjects with AST/ALT $>5 \times$ ULN that persists for more than 7 days (AST/ALT $>8 \times$ ULN for subjects with hepatic involvement);• Subjects with AST/ALT $>20 \times$ ULN that persists for longer than 3 days.• Subjects with Tbili $>3 \times$ ULN that persists for longer than 7 days ($>5 \times$ ULN for subjects with Gilbert's disease).

	Section 8.4.5.
Pretreatment adverse events review	Refer to Section 8.4.5 for guidance on the reporting of adverse events or research-related injuries during the prescreening phase of the study.
For all patients: Submit fresh or adequate archival tumor tissue. Alternatively, prior results from Foundation Medicine may be considered for eligibility with sponsor approval. If patient genetically qualifies based on prior tumor testing submit adequate archival or fresh tissue if available.	Submit tissue from a de novo biopsy of a safely accessible tumor lesion, or archival tumor tissue, for prospective central laboratory enrollment testing. Test results from prior tumor testing identifying DNA repair deficiencies likely to sensitize to PARP inhibition may be considered for eligibility. If sufficient residual DNA is available at Foundation Medicine this could be used to confirm a patient's eligibility for enrollment. Note that if eligibility for enrollment is established based on either prior results or residual DNA testing, available archival or de novo tumor tissue also should be submitted prior to Day 1 to support concordance analyses and additional molecular profiling, unless prohibited by local regulations or ethics committee (EC) decision. Note: biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel <u>may not be</u> performed for the sole purpose of determining study eligibility.
Demographics Prior Anti-Cancer Therapies Medical History- Prostate Cancer	For all patients, including those who by central laboratory assessment are not found to be genetically eligible: <ul style="list-style-type: none">• Obtain patient demographics using the Patient Demographics screening CRF;• Obtain patient prior cancer treatment history using the Prior Cancer Therapy CRF;• Obtain patient prior medical history for prostate cancer using the Medical Prostate History CRF.
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Table 6. Objectives and Endpoints for Study

Primary Objective(s):	Primary Endpoint(s):
To evaluate the efficacy, of single agent talazoparib in DDR+ mCRPC as measured by best objective response rate (ORR).	Best ORR: The proportion of patients with a best overall soft tissue response of CR or PR per RECIST 1.1 by independent central review. Soft tissue responses must be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria by independent central review.
Secondary Objective(s):	Secondary Endpoint(s):
To evaluate efficacy with respect to the following parameters: <ul style="list-style-type: none"> • Time to objective response; • Duration of response; • Proportion of patients with prostate-specific antigen (PSA) decrease $\geq 50\%$; • Proportion of patients with conversion of circulating tumor cell (CTC) count; • Time to PSA progression; • Radiographic progression-free survival (PFS); • Overall survival. 	<p>Time to objective response: The time from first dose of talazoparib to the first objective evidence of soft tissue response with no evidence of confirmed bone disease progression on bone scan per PCWG3. Soft tissue response is defined as a best overall response of CR or PR per RECIST 1.1 by independent central review. The response must be confirmed at least 4 weeks later with a repeated CT/MRI.</p> <p>Duration of response: The time from the first objective evidence of soft tissue response (subsequently confirmed) per RECIST 1.1 by independent central review and no evidence of confirmed bone disease progression per PCWG3 to the first subsequent objective evidence of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is defined as soft tissue progression per RECIST 1.1 by independent central review or bone disease progression per PCWG3 by independent central review.</p> <p>Proportion of patients with PSA response $\geq 50\%$: The proportion of patients with confirmed PSA decline $\geq 50\%$ compared to baseline.</p> <p>For CTC counts:</p> <ul style="list-style-type: none"> • The proportion of patients with conversion of CTC count: The proportion of patients with a CTC count ≥ 5 CTC per 7.5 mL of blood at study entry that decreases to < 5 CTC per 7.5 mL of blood any time on study. • The proportion of patients with a CTC count of 1 or more per 7.5 mL of blood at study entry that decreased to CTC=0 per 7.5 mL of blood any time on study. • The proportion of patients with baseline CTC counts < 5 who show increased CTC counts post-baseline. <p>Time to PSA progression: The time from first dose of talazoparib to the date that a $\geq 25\%$ increase in PSA with an absolute increase of $\geq 2 \mu\text{g/L}$ (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) is documented, confirmed by a second consecutive PSA value obtained ≥ 3 weeks (21 days) later.</p> <p>Radiographic PFS: The time from first dose of talazoparib to radiographic progression in soft tissue per RECIST 1.1 by independent central review, in bone per PCWG3 by independent central review, or death, due to any cause whichever occurs first.</p> <p>Overall survival: Defined as the time from first dose of talazoparib to death due to any cause.</p>

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in [Section 1.2](#)). Talazoparib has cytotoxic effects believed to be caused by inhibition of the catalytic activity of PARP-dependent DNA repair and suppression of DNA synthesis and transcription at sites of PARP trapping.

This study will evaluate patients at prescreening (optional) or screening for DNA damage repair deficiencies as assessed using a biomarker panel of gene mutations. The patients will be evaluated for gene mutations in a panel of genes that, when mutated, are likely to sensitize to PARP inhibition.

The sample size requirement for patients with measurable soft tissue disease supports the primary endpoint of best ORR, which is a clinically relevant endpoint with precedent in oncology indications where high unmet need exists. Cabazitaxel is a possible therapy indicated for these patients and its previous use is permitted. Similarly, radium-233 is a possible therapy for patients with symptomatic bone metastatic CRPC without visceral metastases and its previous use is permitted.

Mechanisms of resistance to PARP inhibition may be shared with DNA-damaging agents such as cyclophosphamide and or mitoxantrone; thus, these agents and prior treatment with a PARP inhibitor in an experimental setting are excluded to maximize the likelihood of treatment efficacy. Similarly, treatment with platinum-based therapies in the 6 months prior to screening, or progression on prior platinum-based therapy at any time in the past, will exclude participation. Treatment with chemotherapy (eg, docetaxel, cabazitaxel) within 28 days of Day 1 and on study is also prohibited given the heightened risk of myelosuppression. A known diagnosis of myelodysplastic syndrome or acute myeloid leukemia and central laboratory hematology values below specified thresholds for hemoglobin, absolute neutrophil count, and platelet count at screening are also exclusionary given the predicted risk of dose-dependent myelosuppression. Pulmonary function testing is not mandated given the rarity of pneumonitis reports with exposure to other PARP inhibitors. Current or anticipated use within 7 days prior to first dose of study drug or anticipated use during the study of strong P-gp inhibitors is exclusionary. For a list of strong P-gp inhibitors, refer to [Section 5.11](#).

C3441006 (MDV3800-06) will include an efficacy assessment schedule of every 8 weeks during the first 24 weeks based on the standard of care for the target patient population with progressive advanced disease. Efficacy assessments will be every 12 weeks after the first 24 weeks. Additional safety precautions will include monitoring for potential hematologic toxicities by evaluating complete blood counts every 2 weeks through week 9, every 4 weeks through week 25, and then every 8 weeks thereafter during treatment. Prolonged myelosuppression will be monitored closely and diagnoses of myelodysplastic syndrome and acute myeloid leukemia occurring during or after study drug treatment will be reported. The potential for liver toxicity will be monitored by periodic transaminase testing with predefined dose modification and discontinuation criteria. Finally, patients with moderate renal impairment will receive talazoparib at a lower starting dose as they are at risk of higher exposure due to decreased renal clearance.

Table 8. Talazoparib Dose Modifications Due to Adverse Events

Toxicity	Management of Adverse Events [1]
Grade 1 or 2 Selected hematologic grade 3 or 4 events	No requirement for dose interruption or dose reduction.
Grade 3 or 4 Anemia (hemoglobin <8.0 g/dL)	<p>Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL or better, then resume talazoparib at a reduced dose per Figure 3.</p> <p>If anemia with hemoglobin <8.0 g/dL recurs after dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL then resume talazoparib at a further reduced dose per Figure 3.</p> <p>If anemia persists for >4 weeks without recovery of hemoglobin to at least 9.0 g/dL despite supportive care measures at any dose level, discontinue talazoparib and consider referral to a hematologist.</p> <p>Transfusions and other supportive measures are permitted to support management of hematological toxicities at any occurrence.</p>
Grade 3 or 4 Neutropenia (ANC <1000/ μ L)	<p>Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC \geq1500/μL, then resume talazoparib at a reduced dose as per Figure 3.</p> <p>If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC \geq1500/μL, then resume talazoparib at a further reduced dose.</p> <p>If neutropenia persists for >4 weeks without recovery to \geq1500/μL at any dose despite supportive care measures, discontinue talazoparib and consider referral to a hematologist.</p> <p>G-CSF and GM-CSF may be used at investigator's discretion for the supportive treatment of neutropenia at any occurrence.</p>
Grade 3 or 4 Thrombocytopenia (platelets <50,000/ μ L)	<p>Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets \geq50,000/μL then resume talazoparib at a reduced dose per Figure 3.</p> <p>If thrombocytopenia (<50,000/μL) recurs after one dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets \geq75,000/μL, then resume talazoparib at a further reduced dose.</p> <p>If thrombocytopenia persists for >4 weeks without recovery to \geq50,000/μL despite supportive care measures, discontinue talazoparib and consider referral to a hematologist.</p> <p>Thrombopoietin analogues and/or platelet transfusions may be used at investigator's discretion for the supportive treatment of thrombocytopenia at any occurrence.</p>

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also [Section 8.1.3 Withdrawal From the Study Due to Adverse Events](#)) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient.

In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved adverse events (AEs). If applicable, patients who return for a final visit will undergo safety and long term follow-up procedures as shown in [Table 3](#) and [Table 4](#).

Patients may withdraw from the study at any time at their own request. If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. If allowed by local laws and regulations survival information will be collected using public records.

Table 10. Primary Reasons for Permanent Treatment Discontinuation

Reason	Comment
Radiographic progression	Per RECIST 1.1 for soft tissue disease and per PCWG3 for bone disease. Must be determined by independent central review and confirmed for bone disease progression. Refer to Section 7.1.2 .
Adverse event or intercurrent illness	Any intolerable adverse event that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the investigator or sponsor would lead to undue risk if study treatment were continued (eg, severe drug-induced liver injury [Section 8.4.2] or MDS/AML]). Refer to Section 8 . May or may not be related to disease progression.
Administration of any systemic anticancer therapy	Refer to Section 5.10 .
Patient decision	Patients may permanently discontinue treatment anytime for any reason. Withdrawal of consent for study treatment should be distinguished from withdrawal of consent for further participation in the study, including follow-up. This category should be selected if adverse event, disease progression, or administration of prohibited concomitant therapy does not apply. Patients are strongly encouraged to continue in long-term follow-up as described in Section 6.6 , even if they choose to permanently discontinue study drug treatment.

7.1.2. Assessment of Radiographic Response and Progression

Disease status will be assessed at regular intervals during the course of the study by CT (chest, abdomen, pelvis), which is the preferred method, or MRI (abdomen, pelvis) of soft tissue, and CT of the chest without contrast if the patient is allergic to CT contrast agents, and whole body radionuclide bone scan. The radiographic assessment of soft tissue disease (including soft tissue components of lytic or mixed bone lesions) will use RECIST 1.1 ([Eisenhauer et al, 2009](#)), and bone disease will be evaluated per PCWG3 ([Scher et al, 2016](#)), with confirmatory imaging requirements shown in Table 11 (modified RECIST1.1/PCWG3). The determinations for study endpoints will be made by independent central review. However, investigator assessments will be collected in the CRF.

Table 11. Confirmatory Imaging Requirements for Soft Tissue per RECIST 1.1 and Bone per PCWG3

Disease Site	Response	Progression
Soft tissue	Must be confirmed at least 4 weeks later ^[1]	No confirmation required ^[1,2]
Bone	Not applicable	Must be confirmed at least 6 weeks later ^[1,2]

1. For analytic purposes.
2. To inform permanent treatment discontinuation.

PCWG3, Prostate Cancer Working Group 3; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

An objective response is defined as a best overall response of CR or PR per RECIST 1.1 by independent central review. Responses must be confirmed by a follow-up CT or MRI at least 4 weeks later and with no evidence of confirmed bone disease progression per Prostate Cancer Working Group 3 (PCWG3) criteria on repeat bone scan at least 6 weeks later by independent central review.

Radiographic assessments will be every 8 weeks through the first 24 weeks, then every 12 weeks thereafter. Scans may be obtained sooner than scheduled if disease progression is clinically suspected (for example, PSA progression). The study films (CT/MRI and bone scan) will be sent for independent central review.

The documentation required for the determination of radiographic progression is shown in [Table 12](#).

A central PSA assessment will be done at screening for all patients.

The screening value must be ≥ 2 ng/mL as assessed at the central laboratory if qualifying solely based on PSA progression. During the study, PSA will be measured at the central laboratory according to the schedule of activities ([Table 3](#)). PSA progression alone should not lead to study drug discontinuation, and study drug administration should continue regardless of PSA increases until radiographic progression is determined by independent central review. PSA progression or response, as determined by the central lab, must be confirmed at least 21 days later.

7.2.2. Assessment of Survival

The survival status of each patient will be monitored during study treatment and after permanent treatment discontinuation for any reason. Survival status will be documented during long-term follow-up according to the schedule of activities ([Table 4](#)). The date and cause of death will be recorded. During the course of the study, the sponsor may request that a survival sweep be conducted to obtain an accurate number of deaths across the study. The sponsor will provide instructions on these survival sweeps immediately before they commence as well as a timeline for contacting patients.

7.2.3. Assessment of Circulating Tumor Cells

The assessment of CTCs will be performed by collecting blood samples according to the schedule of activities ([Table 3](#)). CTC count increases alone should not lead to study drug discontinuation. Details on sample handling and shipping will be provided separately in a laboratory manual.

7.2.4. Assessment of Patient Reported Pain

The assessment of pain will use the BPI-SF. This questionnaire is a validated instrument that uses a self-reported scale assessing level of pain, its effect on activities of daily living, and analgesic medication use. This study will use the short form containing 9 main questions related to pain. The primary question (paraphrased) is “On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours.” The questionnaire is provided in [Appendix 2](#). It is important that patients are fluent in reading the language used in the questionnaire and that they complete it without influence of the investigator, study site staff, or anyone else.

Tracking analgesic use is particularly important to ensure that the delay in pain progression observed is truly the result of the treatment being studied rather than the result of an increase in analgesic use. After the Day 1 visit, pain (assessed using BPI-SF question 3, [Appendix 4](#)) and analgesic use (assessed using an analgesic log, [Appendix 5](#)) will be collected for each of 7 consecutive days prior to study visits; the timing of collection is shown in [Table 3](#) and described in [Section 6.3](#).

7.2.5. Assessment of Patient-Reported General Health Status

The assessment of this patient-reported outcome will use the EQ-5D-5L. The EQ-5D-5L questionnaire is a standardized instrument that measures health-related quality of life for men with prostate cancer. Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self-rate general health state on a scale from “the worst health you can imagine” to “the best health you can imagine.” The EQ-5D-5L questionnaire is provided in [Appendix 3](#).

On Day 1, patients will complete these questionnaires before the first dose of study drug. At subsequent visits, patients will complete these questionnaires at the site before any other study activities and in the same order at each visit. These questionnaires will be collected according to the schedule of assessments in [Section 6.3](#).

7.3. Assessments of Safety

The assessment of safety will include adverse events, physical examinations, vital signs, and clinical laboratory tests. AE will be graded using CTCAE version 4.03. The procedures for the investigator assessment of adverse events are presented in detail in [Section 8](#). The procedures for clinical laboratory safety tests are presented in [Section 7.3.1](#), and for physical examinations and vital signs in [Section 7.3.2](#).

7.3.1. Clinical Laboratory Tests

Routine clinical laboratory tests (hematology, serum chemistry) will be performed according to the schedules of activities by the central laboratory ([Table 2](#), [Table 3](#)). Central safety laboratory assessments may also be collected as unplanned, at the investigator’s discretion, or to monitor adverse events or determine if dosing modifications are required. Local safety laboratory assessments may also be performed but should not replace central lab assessments; results from local laboratory assessments are to be entered in the appropriate CRF. Every effort should be taken to collect samples for central laboratory safety assessments even if unplanned. Samples will be stored until the specified analyses are completed and then will be destroyed in accordance with standard laboratory practice and applicable local regulations.

A list of the required routine clinical laboratory tests and other evaluations is provided below. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to laboratory requirements.

All clinical laboratory tests will be performed by the central laboratory specified in Form FDA 1572 Section 4 unless otherwise specified. The central laboratory reference ranges will be used. Eligibility at screening will be based on central laboratory assessments (preceding local laboratory PSA values will also be required if qualifying based solely on PSA progression). The screening value must be ≥ 2 ng/mL as assessed at the central laboratory if qualifying solely based on PSA progression.

A local clinical laboratory may be used to evaluate serum chemistry and hematology within 3 days before a scheduled visit. The results of these local laboratory assessments may be used for dosing decisions. However, samples must also be collected and sent to the central laboratory for testing.

For all patients, a local clinical laboratory may be used to assess samples at unscheduled visits or for urgent care to evaluate an adverse event. Central laboratory samples should also be obtained whenever possible during unscheduled visits.

Central Laboratory Tests

Hematology	Chemistry	Additional
Hematocrit	Albumin	PSA (prostate-specific antigen)
Hemoglobin	Total protein	Testosterone (screening only)
Mean corpuscular volume	Alkaline phosphatase	
Red blood cell count	ALT (alanine aminotransferase)	
Platelet count	AST (aspartate aminotransferase)	
	Total bilirubin	
White blood cell count with differential	Blood urea nitrogen	
Total neutrophils	Creatinine	
Lymphocytes	Glucose (nonfasting)	
Monocytes	Bicarbonate	
Eosinophils	Calcium*	
Basophils	Chloride	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	LDH (lactate dehydrogenase)	

The laboratory manual for this study provides details regarding sample collection procedures, laboratory tests, and additional tests that may be required. *Central lab data include calcium and calcium albumin corrected.

7.3.2. Physical Examinations, Vital Signs, and ECGs

The investigator will perform physical examinations according to the schedules of activities ([Table 2](#), [Table 3](#)). Interval medical history will be reviewed as a part of physical examinations. Physical examinations will include an assessment of systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms. Weight will be measured at the time of the examination. Height will be measured only at screening. Vital sign measurements will include blood pressure, heart rate, and temperature.

12-Lead ECGs will be obtained and read locally at screening. Additional ECGs may be obtained as necessary per standard of care.

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As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient/legally acceptable representative. In addition, each study patient/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the [Permanent Treatment Discontinuation Section](#))

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study or treatment because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the [Requirements](#) section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed consent, which is obtained before the patient’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

A different reporting period applies only to patients who sign the molecular prescreening consent as described in [Section 8.4.5](#).

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form as of signing of the main informed consent document (ICD) at screening.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety. All SAEs of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) are to be reported to Pfizer Safety irrespective of investigator's opinion of causality or time of diagnosis.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

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.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms only of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) Grade 5 (see the [Severity Assessment](#) section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor. The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels.

Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Although this study will be conducted exclusively in male patients, it is theoretically possible for female partners to be exposed to study drug during pregnancy. Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

An investigator may be requested by the designated Pfizer clinician to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Record research-related injuries on the CRF from the time the patient undergoes a procedure until the patient is deemed a screen failure or until the end of the study.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical and Analysis Plans

The statistical methods and analyses for this study will be described in detail in the statistical analysis plan. Three analyses are planned, including an initial safety analysis/efficacy analysis followed by two efficacy analyses. The initial safety/efficacy analysis will be performed after 20 patients with measurable soft tissue disease and DDR deficiencies likely to sensitize to PARP inhibitor therapy have received the study drug for at least 8 weeks. Efficacy analyses of the primary endpoint will also be performed when 60 and 100 patients have completed at least 6 months of study treatment or are no longer being followed (ie, have withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up).

9.2. Analysis Populations

The DDR Deficient Measurable Disease population is defined as all enrolled patients who have measurable soft tissue disease at screening by ICR, have DDR deficiencies likely to sensitize to PARP inhibitor therapy and receive at least one dose of talazoparib. The DDR Deficient Measurable Disease population will be used for all baseline characteristics summaries and efficacy analyses.

Summaries and listings of efficacy and baseline data for patients that were enrolled under previous protocol versions and who are not part of the DDR Deficient Measurable Disease population will be described in the statistical analysis plan.

The safety population is defined as all patients who receive at least one dose of talazoparib. The safety population will be used for all safety analyses.

The PK population is defined as all patients from the safety analysis set who have at least 1 reportable drug concentration data point.

independent central review or bone disease progression per PCWG3 by independent central review. Details on the conventions for censoring will be presented in the statistical analysis plan. Analyses will include the patients from the DDR Deficient Measurable Disease population who achieve a confirmed CR or PR without documentation of confirmed bone progression. Duration of response will be estimated using the Kaplan-Meier method and 95% CI for median time will be calculated using the Brookmeyer-Crowley method ([Brookmeyer & Crowley, 1982](#)). Analyses based on assessment by the investigator will also be performed.

9.3.2.3. Proportion of Patients With PSA Response $\geq 50\%$

PSA response will be calculated as a decline from baseline PSA (ng/mL) by at least 50% measured by central laboratory. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. Patients without a baseline and at least one post baseline PSA assessment will not be analyzed for this endpoint. Only assessments performed from the date of first dose of study treatment until confirmed PSA progression or start of new anticancer treatment given after the first dose of study treatment will be considered. The proportion of patients in the DDR Deficient Measurable Disease population with confirmed PSA decline $\geq 50\%$ compared to baseline will be calculated along with the 95% CI using the Clopper-Pearson method ([Clopper-Pearson; 1934](#)).

9.3.2.4. CTC Count Conversion Rate

The CTC count conversion rate will be defined as the proportion of patients with a CTC count ≥ 5 CTC per 7.5 mL of blood at study entry that decreases to < 5 CTC per 7.5 mL of blood anytime on study. CTC counts < 5 CTC per 7.5 mL of blood will be considered favorable and CTC counts ≥ 5 CTC per 7.5 mL of blood will be considered unfavorable. The conversion rate will be calculated along with the 95% CI using the Clopper-Pearson method ([Clopper-Pearson; 1934](#)). Patients with a CTC count < 5 per 7.5 mL of blood at baseline are not analyzed for this conversion endpoint, though they are included in continuous summaries. In addition, the proportion of patients with a CTC count of 1 or more (detectable) per 7.5 mL of blood at study entry that decreased to CTC=0 (undetectable) per 7.5 mL of blood any time on study will be assessed. The conversion rate will be calculated along with the 95% CI using the Clopper-Pearson method ([Clopper-Pearson; 1934](#)). Patients with a CTC count of 0 per 7.5 mL of blood at baseline are not analyzed for this conversion endpoint, though they are included in continuous summaries. The proportion of patients with baseline CTC counts < 5 who show increased CTC counts post-baseline will also be assessed.

9.3.2.5. Time to PSA Progression

The time to PSA progression is defined as the time from first dose of talazoparib to the date that a $\geq 25\%$ increase in PSA with an absolute increase of $\geq 2 \mu\text{g/L}$ (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) is documented, confirmed by a second consecutive PSA value obtained ≥ 3 weeks (21 days) later. Kaplan-Meier estimates will be presented together with a summary of associated statistics including the median and quartiles with two-sided 95% CIs. Conventions for censoring will be presented in the statistical analysis plan.

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9.7. Determination of Sample Size

At least 100 patients will be enrolled with soft tissue measurable disease (per RECIST1.1) and alterations in DNA damage repair genes, determined at prescreening (optional) or screening by the gene mutation biomarker panels used for the assessment of tumor tissue DNA.

- Patients with DNA damage repair deficiencies assessed using the gene mutation biomarker panels used for the assessment of a panel of genes likely to sensitize to PARP inhibition (N = 100).

With 100 patients the ORR can be estimated with a maximum standard error of 5.1%. A sample size of 100 patients is sufficient to demonstrate that if the observed best ORR is $\geq 23\%$, the lower bound of the corresponding exact 2-sided 95% CI excludes 15.2%.

Table 14 provides the response rates and exact 95% CI for 100 patients based on different scenarios.

Table 14. Response Rates and Exact 95% CI for 100 Patients

Number of Responders	ORR point Estimate	Lower 95% CI of ORR	Upper 95% CI of ORR
23	23%	15.2%	32.5%
33	33%	23.9%	43.1%
43	43%	33.1%	53.3%
50	50%	39.8%	60.2%

9.8. Interim Analysis

The study is designed to have an initial analysis for safety and efficacy and an interim analysis for efficacy. The initial analysis will be performed after 20 patients from the DDR deficient measurable disease population receive study treatment for at least 8 weeks. The subsequent interim analysis will be performed when 60 patients form the DDR deficient measurable disease population complete at least 6 months of study treatment or are otherwise no longer being followed (ie, have, withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up).

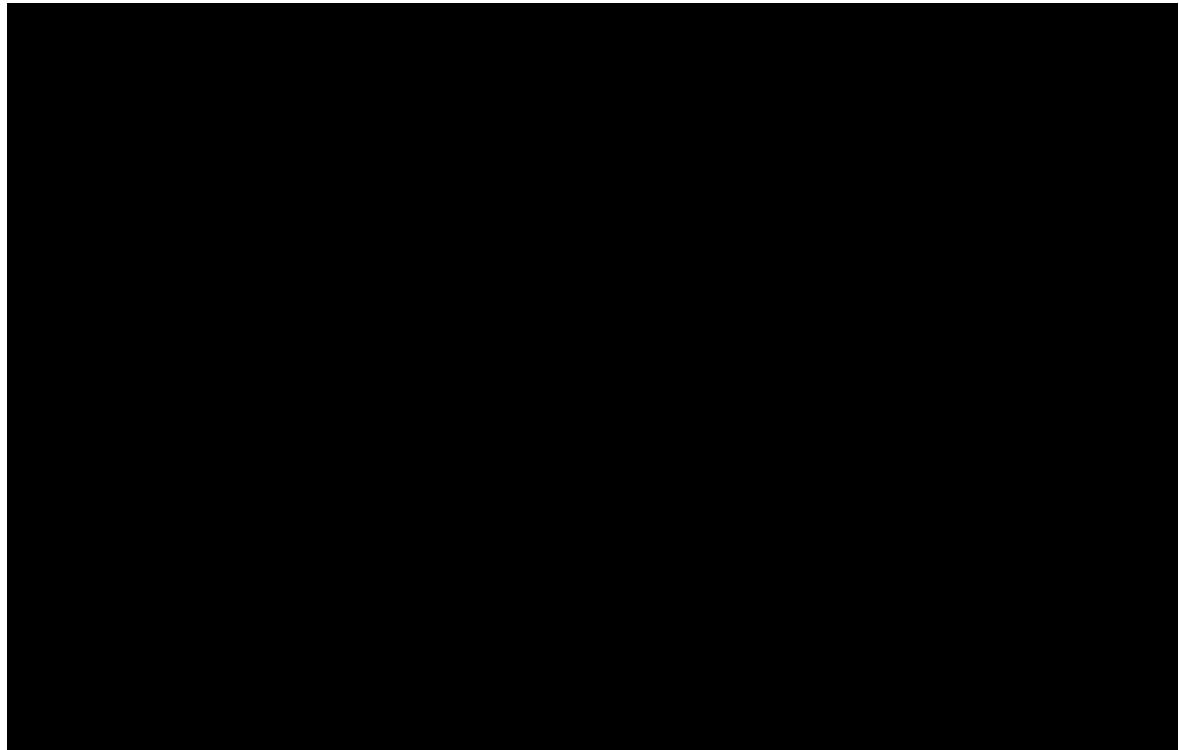
An interim analysis with at least 60 patients is planned and if the observed best ORR is $\geq 23\%$, the lower bound of the corresponding exact 2-sided 95% CI would exclude $< 13\%$.

With 60 patients, the ORR can be estimated with a maximum standard error of 6.6%. Table 15 provides the exact binomial 95% CI for ORR for 60 patients based on different observed responses.

Table 15. Response Rates and Exact 95% CI for 60 Patients

Number of Responders	ORR point Estimate	Lower 95% CI of ORR	Upper 95% CI of ORR
14	23.3%	13.4%	36%
20	33.3%	21.7%	46.7%
26	43.3%	30.6%	56.8%
30	50%	36.8%	63.2%

Abbreviation	Term
EQ-5D-5L	European Quality of Life 5-Dimension, 5-Level Scale
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GnRH	gonadotropin-releasing hormone
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNPC	hormone-naïve prostate cancer
HR	hazard ratio
HRD	homologous recombination deficiency
HRQL	health-related quality of life
IC50	half -maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICD	informed consent document
ICR	independent central review
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K ₂ EDTA	dipotassium ethylenediaminetetraacetic acid
Ki	inhibitory constant
LFT	liver function test
LPLV	last patient last visit
M0	nonmetastatic
M1	metastatic
mCRPC	Metastatic castration-resistant prostate cancer
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndrome
MDV	Medivation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NAD	nicotinamide adenine dinucleotide
NASH	Nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next generation sequencing
NHT	novel hormonal therapy
NLCB	no longer clinically benefitting



Section 8 for details). Report any diagnosis of MDS or AML as an SAE any time after the first dose of talazoparib (Section 8.1.4.1 and Section 8.2.3). AEs and SAEs will be followed until the event or its sequelae resolves or stabilizes at a level acceptable to the investigator and the sponsor concurs with that assessment.

9. Instruct patient to self-administer talazoparib. The first dose is taken in the clinic; record the exact time of dose.
10. Refer to the central laboratory instruction manual for sample processing and for estimated turnaround time for laboratory results.
11. Central laboratory assessments (safety) are to be done at every scheduled visit, as well as unplanned, at the investigator's discretion, or to monitor adverse events or decide dosing modifications, noting that local safety assessments may also be performed but should not replace central lab assessments. Every effort should be taken to collect samples for central laboratory safety assessments even if unplanned. If serum chemistry and hematology laboratory tests were also done locally due to logistical issues, results from local laboratory assessments are to be entered in the appropriate CRF.
12. Collect blood samples for talazoparib PK at predose and 2 hours postdose in Week 1 (Day 1) and in Week 5, and predose in Weeks 9 and 13. Additional PK samples could be taken based on discretion of investigators, eg, adverse events. The actual time of the sample collection and the most recent dosing time before and after each collection will be recorded on the CRF.
13. Blood sample for CTC enumeration. Collect a minimum of 10 mL of whole blood at indicated visits. CTC samples must be shipped on day of collection and at room temperature. See Section 7.5 and Central Laboratory Manual.

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1.2. Background and Rationale

1.2.1. Prostate Cancer

Prostate cancer is the second leading cause of cancer death in men. The American Cancer Society estimates that up to 180,890 men in the United States (US) will be diagnosed with prostate cancer and approximately 26,120 will die of the disease in 2016 ([American Cancer Society, 2016](#)). In Europe in 2012, prostate cancer was the third most common cancer site, with an estimated 416,700 new cases and 92,200 deaths ([Ferlay et al, 2013](#)).

The androgen receptor signaling axis, the principal driver of prostate cancer growth, has long been targeted by castration. However, a proportion of tumors progress despite castrate levels of testosterone, at which point the disease is considered castration-resistant.

Castration-resistant prostate cancer (CRPC) represents a lethal transition in the progression of prostate cancer, with most patients ultimately succumbing to the disease. Molecular profiling studies have revealed that the androgen receptor remains functional in a majority of progressing tumors. Rationally designed therapies targeting the androgen receptor signaling pathway ([Donovan et al, 2010](#)) include enzalutamide, a novel androgen receptor antagonist that is active in the presence of androgen receptor overexpression ([Tran et al, 2009](#)), and abiraterone acetate/prednisone ([de Bono et al, 2011](#)), an inhibitor of 17,20-lyase (an androgen biosynthetic enzyme overexpressed in CRPC) ([Stanbrough et al, 2006](#); [Holzbeierlein et al, 2004](#)). Prior to the recent approval of novel hormonal therapies (NHT) (enzalutamide, abiraterone acetate/prednisone), the only approved therapies for metastatic CRPC were docetaxel, cabazitaxel and sipeleucel-T. The approval of NHTs in metastatic CRPC previously treated with docetaxel ([De Bono et al, 2011](#); [Scher et al, 2012](#)) represented a therapeutic advance for these patients.

Clinical experience with these therapies validated findings that the androgen receptor remains active despite androgen deprivation in men with CRPC, but resistance to these second-generation agents invariably occurs. Median survival remains low (approximately 15-18 months) for men with metastatic CRPC who had previously received docetaxel in studies of enzalutamide and abiraterone acetate/prednisone ([Scher et al, 2012](#); [de Bono et al, 2011](#)). Furthermore, in the COMET-1 study of men with metastatic CRPC who had previously received both docetaxel and novel hormonal therapy, the median survival for those who received cabozantinib or prednisone was even lower at 11.0 months and 9.8 months, respectively ([Smith et al, 2015](#)). No approved therapy has been tested in the target population of this study, as all currently approved treatments for symptomatic metastatic CRPC (including soft tissue disease) after docetaxel-based chemotherapy were tested in patients who had not received novel hormonal therapy. Thus, the target population in this study has an unmet medical need deserving of potentially promising experimental therapies.

The key efficacy results of phase 2 and 3 studies in metastatic CRPC after chemotherapy (primarily docetaxel) are presented in [Table 5](#).

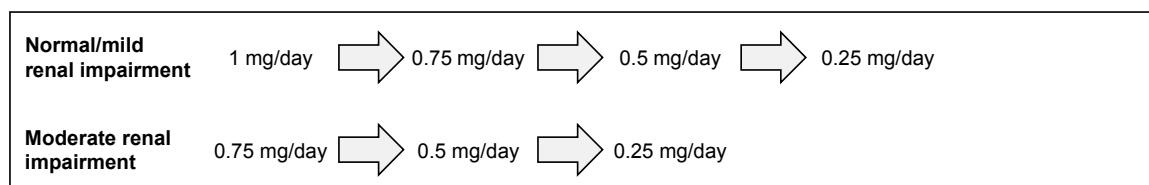
Table 8. Talazoparib Dose Modifications Due to Adverse Events

Toxicity	Management of Adverse Events [1]
Nonlaboratory grade ≥ 3 events ^[1]	<p>Hold talazoparib as follows:</p> <p>For clinically significant grade 3 adverse events, hold talazoparib until the adverse event resolves to grade ≤ 1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level per Figure 3.</p> <p>For clinically significant grade 4 adverse events, hold talazoparib until the adverse event resolves to grade ≤ 1 or baseline. Resume talazoparib at a 1 dose level reduction per Figure 3.</p> <p>Implement supportive care per local guidelines. Contact sponsor to discuss potential dose modification.</p> <p>Talazoparib must be permanently discontinued for unresolved grade 3 toxicity lasting longer than 4 weeks or for grade 4 toxicity lasting longer than 1 week.</p> <p>Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the sponsor. Talazoparib must be discontinued if a grade 4 adverse event recurs after treatment resumes.</p>

1. Talazoparib dose re-escalation may be allowed after the reduced dose is tolerated without recurrence of toxicities, and after discussion with the sponsor. AML, acute myeloid leukemia; ANC, absolute neutrophil count; MDS, myelodysplastic syndrome.

The dose of talazoparib may be reduced incrementally as shown in Figure 3:

Figure 3. Talazoparib Dose Reduction for Toxicity



Dose re-escalation: Dose re-escalation may be allowed after toxicities resolve, the reduced dose has been tolerated, and after discussion with the sponsor.

5.7. Treatment Compliance

Accountability for the study drug capsules will be performed to document compliance with the dosing regimens. Patients will be asked to bring all used and unused study drug bottles to study visits for personnel to perform drug accountability prior to dispensing additional study drug. Study site personnel must make reasonable efforts to obtain used and unused study drug bottles from patients who do not routinely return them at study site visits. Unreturned capsules will be considered to have been taken.

5.8. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all talazoparib is stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

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Figure 2 (below).

Talazoparib 1 mg/day was determined to be the maximum tolerated dose (MTD) and recommended phase 2 monotherapy dose based on the results of the phase 1, dose-escalation study in patients with solid tumors, PRP-001. Based on population PK analyses, talazoparib CL/F was estimated to be 37.1% lower in patients with moderate renal impairment than in those with normal renal function, resulting in higher exposure ([Section 1.3.3](#)). Simulations were performed to predict the steady-state exposure (AUC) for a 0.75 mg/day dose in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m²) and for a 1 mg/day dose in patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m²) (Table 7). The predicted exposure at 0.75 mg/day for patients with moderate renal impairment is comparable to the exposure at 1 mg/day for patients with normal renal function as assessed by steady-state AUC. Based on these data, the planned starting dose for patients with moderate renal impairment is 0.75 mg/day. Patient with moderate renal impairment should remain on a reduced talazoparib dose throughout the study; dose escalation to a dose of 1 mg/day is not permitted for those patients.

Table 7. Predicted Talazoparib Mean Exposure at Steady-State

Renal Function	Dose (mg/day)	Steady-State AUC ₀₋₂₄ (ng•h/mL) Mean (5 th -95 th Percentile)
Normal	1	161 (136-188)
Moderate impairment	0.75	179 (163-196)

AUC₀₋₂₄, area under the plasma concentration-time curve from time zero to the time 24 hours (dosing interval).

4. PATIENT ELIGIBILITY CRITERIA

Selection of Study Population

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

The specific eligibility criteria for selection of patients are provided in [Section 4.1](#) and [Section 4.2](#). The sponsor will not grant any eligibility waivers.

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Patients must be at least 18 years of age, and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

Table 10. Primary Reasons for Permanent Treatment Discontinuation

Reason	Comment
Investigator decision	Protocol treatment may be discontinued if the investigator considers it is in the patient's best interest. This category should be selected if adverse event, disease progression, or administration of prohibited concomitant therapy does not apply and the patient preferred to continue treatment.
Major noncompliance with protocol	The sponsor or investigator may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.
Lost to follow-up	Refer to Section 6.7 .
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime for any reason as described in Section 14 . The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

6.5. Safety Follow-up

Patients will have safety follow-up after permanent discontinuation of study drug treatment. Safety follow-up should occur approximately 28 days after the last dose of study drug or before initiation of new antineoplastic or investigational therapy, whichever occurs first. In the event that new antineoplastic or new investigational therapy is initiated before safety follow-up occurs (eg, a physician not associated with protocol C3441006 (MDV3800-06) initiates the treatment, and study site personnel are not aware of the treatment until afterward), safety follow-up should be scheduled as soon as possible.

Safety follow-up procedures are listed in [Table 3](#).

If treatment is discontinued due to an adverse event or serious adverse event, the event(s) must be followed up as described in [Table 3](#).

For patients who refuse to come to the clinic for safety follow-up, telephone contact must be attempted and documented to review for adverse events through approximately 28 days after the last dose of study drug or before initiation of new antineoplastic or new investigational therapy, whichever occurs first. If the patient does not respond to telephone calls, the procedures for lost to follow-up in [Section 6.7](#) should be followed.

6.6. Long Term Follow up

For long-term follow-up procedures see [Table 4](#). This period begins after safety follow-up and can be conducted by telephone unless imaging is required. Long-term follow-up begins after safety follow-up and continues until the patient dies, withdraws consent or, refuses follow up, or the study is terminated. Radiographic imaging should continue during long-term follow-up for patients who discontinue study drug for any reason other than radiographic progression, determined by independent central review, when the patient has not withdrawn consent for follow-up. All known follow-up anticancer therapies have to be entered in the CRF. Potential cases of AML or MDS will be entered in the CRF and reported as SAEs in the sponsor safety database irrespective of investigator's opinion of causality or time of diagnosis.

Table 12. Criteria for Evidence of Radiographic Progression

Date Progression Detected (Visit) ^[1]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 9	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3.	Timing: at least 6 weeks after progression identified or at week 17 visit. ^[2]	Persistence of at least two of the lesions seen at week 9 AND 2 or more additional new bone lesions on bone scan compared to week 9 scan (2+2 rule). Date of progression is the date of the first post treatment scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	No confirmatory scan required for soft tissue disease progression.
Week 17 or later	Bone lesions: 2 or more new lesions on bone scan compared to <u>week 9 bone scan</u> .	Timing: at least 6 weeks after progression identified or at next imaging time point. ^[2]	At least 2 of the lesions first identified as new compared to week 9 must be still present. Date of progression is the date of the scan that first documented 2 or more new lesions.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	No confirmatory scan required for soft tissue disease progression.

1. Progression detected by bone scan at an unscheduled visit either before week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.

2. Confirmation must occur at the next available scan.

CT, computed tomography; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Working Group 3; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

7.2. Assessments of Secondary Efficacy Endpoints

The secondary efficacy endpoints include time to objective response, duration of response, proportion of patients with PSA response $\geq 50\%$, proportion of patients with conversion of CTC count, time to PSA progression, radiographic PFS, overall survival. The study assessments of efficacy for these endpoints will include standard radiographic and imaging methods to evaluate disease progression and response, PSA, survival status monitoring, pain and quality of life questionnaires, and CTC enumeration.

7.2.1. Assessment of PSA

Local laboratory PSA values will be used to determine eligibility for the study at screening (**Table 2**) including a minimum of 3 consecutive, rising PSA values with an interval of at least 1 week between determinations; values are to be recorded on the CRF. The third PSA may or may not be the central lab screening PSA. (If the screening central lab PSA is lower than local lab PSA #2, then a third local lab PSA may be submitted instead if the PSA measurement is higher than the second local lab PSA.)

Table 3). Additional PK blood samples may be collected from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation. Plasma talazoparib concentrations will be measured using a validated method.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time AND collected prior to administration of the investigational product on that day (for pre-dose PK samples) will be considered protocol compliant. Patients must be instructed to withhold their daily dose of study drugs on PK sampling days until the pre-dose PK sample collection has been completed. The actual time of the sample collection and the most recent dosing time before and after each collection will be recorded on the CRF. The date of missing dose should also be recorded in the CRF.

Samples will be collected, processed and shipped as described in the laboratory manual.

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Table 2, Table 3). Scoring for the assessment is shown in Table 13.

Table 13. ECOG Performance Status

Score	Description of Functional Status
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

Source: Oken et al, 1982

ECOG, Eastern Cooperative Oncology Group.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

The investigator will use the following definitions of severity in accordance with the current CTCAE version (4.03) to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products);
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy;
- If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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Clopper-Pearson; 1934). Analyses based on assessment by the investigator will also be performed.

9.3.2. Secondary Efficacy Analyses

The following efficacy parameters will be evaluated.

9.3.2.1. Time to Objective Response

The time from first dose of talazoparib to the first documented objective evidence of soft tissue response with no evidence of confirmed bone disease progression on bone scan per PCWG3. Soft tissue response is defined as a best overall response of CR or PR per RECIST 1.1 by independent central review. The response must be confirmed at least 4 weeks later with a repeated CT/MRI. Analyses will include the patients from the DDR Deficient Measurable Disease population who achieve a confirmed CR or PR without documentation of confirmed bone progression. Descriptive statistics (mean, standard deviation, median, minimum, maximum, and quartiles) will be provided. Analyses based on assessment by the investigator will also be performed.

9.3.2.2. Duration of Response

The duration of response is defined as the time from the first objective evidence of soft tissue response (subsequently confirmed) per RECIST 1.1 by independent central review and no evidence of confirmed bone disease progression per PCWG3 to the first subsequent objective evidence of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is defined as soft tissue progression per RECIST 1.1 by

9.3.2.6. Radiographic PFS

Radiographic PFS is defined as the time from first dose of talazoparib to radiographic progression in soft tissue per RECIST 1.1 by independent central review, in bone per PCWG3 by independent central review, or death due to any cause, whichever occurs first. Details on the conventions for censoring PFS will be presented in the statistical analysis plan. Radiographic PFS will be estimated using the Kaplan-Meier method; the 95% CI for median time will be calculated using the Brookmeyer-Crowley method ([Brookmeyer & Crowley, 1982](#)). Analyses based on assessment by the investigator will also be performed.

9.3.2.7. Overall Survival

Overall survival is defined as the time from first dose of talazoparib to death due to any cause. Details on the conventions for censoring will be presented in the statistical analysis plan. Kaplan-Meier methods will be used to estimate overall survival. The 95% CI for median overall survival time will be calculated using the Brookmeyer-Crowley method ([Brookmeyer & Crowley, 1982](#)).

9.3.2.8. Patient Reported Pain

Pain assessed by the BPI-SF will be summarized using descriptive statistics by study visit.

Patient-reported outcomes assessments will be analyzed using the PRO population. Missing items will be handled per the scoring manuals of each questionnaire administered.

Deterioration in pain is defined as ≥ 2 -point increase from baseline using question 3 of the BPI-SF. Additional pain and analgesic assessments will be completed for 7 consecutive days before study visits. Four or more completed daily pain reports at each reporting time period are required for a patient to be considered evaluable. Pain score averages during each reporting period will be calculated.

In order to adequately measure pain, it is equally important to adequately track analgesic use to ensure that the pain palliation observed is not the result of an increase in analgesic use but rather the effect of the antitumor treatment being studied. Analgesic data (from the analgesic log) will be mapped to the WHO analgesic usage score and used concurrently to define pain progression with the BPI SF ([Basch E et al, 2013](#)).

Time to deterioration in pain will be summarized using the Kaplan-Meier method and will include the median and 95% CIs based on the Brookmeyer-Crowley method. Longitudinal mixed effects model analyses will be used to assess change from baseline in pain symptoms.

9.3.2.9. Patient-Reported General Health Status (and Health Index)

A patient-reported general health status assessed by the EQ-5D-5L will be summarized using descriptive statistics. Longitudinal mixed effects model analyses will be used to assess change from baseline in general health status. In addition, there will be a health status profile analysis consisting of a display of the number and percentage of patients in each of the 5 response levels for each of the 5 dimensions at each visit.

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.9. Data Monitoring Committee

This study will not use a Data Monitoring Committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

Abbreviation	Term
NSAIDS	Nonsteroidal anti-inflammatory drugs
ORR	Objective response rate
P-gp	P-glycoprotein
PARP	poly(adenosine diphosphate-ribose) polymerase
PCD	primary completion date
PCT	Physician's choice chemotherapy
PCWG	Prostate Cancer Working Group
PD	pharmacodynamics(s)
PF	Pfizer
PFS	progression-free survival
PGx	pharmacogenomics(s)
PI	principal investigator
PID	patient identification
PK	pharmacokinetic
PR	partial response
PR-25	Quality of Life Questionnaire Prostate Cancer Module
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time
QoL	quality of life
QLQ-C30	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCLC	Small cell lung cancer
SMQ	Standardized MedDRA Query
SOP	standard operating procedure
SRSD	single reference safety document
SSID	single subject identification
SUSAR	suspected unexpected serious adverse reaction
SPARC	Satraplatin and Prednisone Against Refractory Prostate Cancer;
TALAPRO	TALAzoparib PROstate
TBili	total bilirubin
TEAE	treatment-emergent adverse event
Tmax	Time to mean maximum plasma concentration
TOPARP-A	Trial of Olaparib in Patients With Advanced Castration Resistant Prostate Cancer, part A
ULN	upper limit of normal
US	United States
V/F	volume of distribution
WHO	World Health Organization

