Janssen Research & Development *

Clinical Protocol

A Phase 2 Efficacy and Safety Study of Niraparib in Men with Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies

Protocol 64091742PCR2001: The Galahad Study; Phase 2

AMENDMENT 8

JNJ-64091742 (niraparib)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Amendments below are listed beginning with the most recent amendment.

Amendment 8 (17 July 2020)

The overall reasons for the amendment: (1) to add a Long-term Extension Phase, (2) to include subjects who have germline pathogenic BRCA (BRCA1 or BRCA2) mutations in the efficacy analyses, and (3) to provide updated patient enrollment recruitment requirements.

Applicable Section(s)	Description of Change(s)
Rationale: To allow subjects who are benefiting from therapy to continue to receive niraparib after the primary analysis is completed.	
Synopsis (Overview of Study Design); Time and Events Schedule; 3. Study Design; 9.1.7. Long-term Extension Phase; 10.2. Withdrawal from the Study; 16.2.3. Informed Consent; Attachment 7	Attachment 7 outlines the criteria for participation and procedures to be performed in the Long-term Extension Phase. Added the option for remote/virtual consenting.
Rationale: To align the analysis population with the protocol entry criterion 7.2.b. that allows subjects with germline pathogenic BRCA1 or BRCA2 mutations to enroll.	

Applicable Section(s)	Description of Change(s)
Synopsis (Objectives, Endpoints/Assessments, and Hypothesis, Overview of Study Design, Statistical Methods); 2.1. Objectives and Endpoints/Assessments; 3. Study Design; 9.7. Biomarkers; 11.1. Analysis Populations; 11.3. Efficacy Analyses;	Added text indicating that subjects who have germline pathogenic BRCA (BRCA1 or BRCA2) mutations will be included in the efficacy analyses.
Rationale: The current number of planned subjects has been updated.	
Synopsis (Overview of Study Design); 3. Study Design; 11.2. Sample Size Determination	Specified that the study will assess up to approximately 120 subjects with measurable disease, at least 75 subjects with BRCA (BRCA1 or BRCA2) mutations and 45 subjects with non-BRCA DNA-repair anomalies, and that an additional cohort of at least 90 subjects with non-measurable disease will be included. The sample size estimates were adjusted accordingly.
Rationale: To align with niraparib core safety information.	
6.2.1. Non-hematologic Toxicities 10.1. Discontinuation of Study Treatment	Added treatment-related hypertensive crisis or posterior reversible encephalopathy syndrome as conditions for which subject's study treatment must be discontinued.
Rationale: To align with current internal protocol template.	
12.3.4. Disease Progression and Death	Instructions for reporting disease progression and death have been updated.
Attachment 6: Anticipated Events	Instructions for reporting and assessing anticipated events have been updated.
<u>COVID-19 Appendix</u> (17 April 2020) **The overall reason for the appendix:** to provide study-related guidance during the global coronavirus (COVID-19) pandemic.	

Applicable Section(s)	Description of Change(s)
Rationale: For health and safety reasons, subjects may not be able to come to the study site for scheduled procedures.	
COVID-19 Appendix	The standalone Appendix provides guidance to investigators for managing study-related procedures during the COVID-19 pandemic.
<u>Amendment 7</u> (30 October 2019)	

The overall reason for the amendment: is to allow subjects with local germline pathogenic results for Breast Cancer gene 1 (BRCA1) or Breast Cancer gene 2 (BRCA2) DNA-repair defects (DRD) to enter the trial given the high likelihood of biallelic mutations.

Applicable Section(s)	Description of Change(s)
Rationale: As the enrollment was nearing completion to the anticipated number for subjects with non-measurable disease (irrespective of mutational status), the number of subjects with non-measurable disease was increased to allow continued enrollment of such subjects up to an increased target number.	
Synopsis (Overview of Study Design, Statistical Methods); 3. Study Design; 11.2. Sample Size Determination	Minor edits made to indicate the study will assess up to approximately 155 subjects with measurable disease who are biomarker-positive (blood- or tissue-based assay), and at least 60 subjects with non-measurable disease, regardless of DNA anomaly.
Rationale: Subject population clarified via notation of types of DNA-repair anomalies to allow inclusion of subjects with local-test assessed germline pathogenic BRCA1 or BRCA2 mutations. Also include modifications to Prescreening Eligibility Criteria and Inclusion Criteria to align with previous Amendment that reflected the current clinical practice for the treatment of patients with metastatic prostate cancer based on protocol steering committee feedback and to reflect the characteristics of the third line mCRPC population.	
4. Subject Population	Text was updated as follows (deletions appear in overstrike, new text in bold): Male subjects over the age of 18 years with mCRPC and DNA-repair anomalies **(biallelic mutations and germline pathogenic mutations only for BRCA1 or BRCA2 mutations)** who received ~~a~~ **prior** taxane-based chemotherapy and AR-targeted therapy **(second-generation or later)** ~~for the treatment of metastatic prostate cancer~~ are eligible for the study.
4.1. Prescreening Eligibility Criteria (Criterion 3.3)	Text was updated as follows (deletions appear in overstrike, new text in bold): Must **have received or** be **currently** on **at least 1 taxane-based chemotherapy** ~~or after second-line of treatment~~ for ~~mCRPC~~ **metastatic prostate cancer and at least 1 AR-targeted (second-generation or later) therapy**.
4.2. Inclusion Criteria (Criterion 6.5 and 7.2)	Text was updated as follows (deletions appear in overstrike, new text in bold): Received **a second-generation or later** AR-targeted therapy (for example, abiraterone acetate plus prednisone, enzalutamide, apalutamide) for the treatment of metastatic prostate cancer with evidence of disease progression **or non-metastatic castration-resistant prostate cancer with evidence of subsequent metastasis**. Criterion 7.1 was modified (now noted as Criterion 7.2): Biomarker-positive ~~for DNA-repair anomalies~~ **by at least one of the following criteria** (~~S~~see Section 9.7): **a. Biallelic DNA-repair anomaly (refer to Table 5) based on a sponsor-validated blood or tissue assay.** **b. Germline pathogenic BRCA1 or BRCA2 by any test (somatic local results must be confirmed as positive by the sponsor-validated assay before dosing).**
9.7. Biomarkers	Text edited to characterize the primary efficacy population (ie, subjects confirmed to be biallelic BRCA1 or BRCA2 by a sponsor-validated blood-or tissue-based assay).

Applicable Section(s)	Description of Change(s)
11.1. Analysis Populations	Text was updated as follows (deletions appear in overstrike, new text in bold): Enrolled Population: All subjects who are enrolled into the study. This population will be used for **exploring efficacy/anti-tumor activity**, subject disposition and biomarker analyses. **Primary Efficacy**~~ITT~~ Population: All subjects who **received at least 1 dose of study drug, had**~~have~~ biallelic **BRCA1 or BRCA2** ~~DNA repair anomalies as determined by a~~ **per the** sponsor-validated blood- or tissue-based assay. ~~This population will be used for efficacy analyses.~~
Rationale: Revisions were made to rename the "intent-to-treat (ITT) Population" as the "Primary Efficacy Population"; to define study phases, biomarker panel collection periods, samples for collection, timing of when subjects can enter the treatment phase, and criteria for biomarker-positivity.	
Synopsis (Overview of Study Design); 3. Study Design	Minor modifications made to describe the 4 study phases.
Synopsis (Overview of Study Design, Subject Population); 4. Study Population	Minor edits to text, including clarification of when subjects received taxane-based chemotherapy and androgen receptor (AR)-targeted therapy.
Synopsis (Biomarker Evaluations)	Minor edits made regarding the use of whole blood for RNA and circulating tumor DNA.
Time and Events Schedule	The biomarker panel will be collected during either the Prescreening or Screening phases.
11.1. Analysis Populations; 11.3. Efficacy Populations	Renamed the ITT Population as the Primary Efficacy Population.
Time and Events Schedule (Tablenotes b, c, and d)	Text was updated as follows (deletions appear in overstrike, new text in bold): b. Biomarker panel: Blood **and tissue** samples will be collected for evaluation of biomarker-positivity during the Prescreening **or Screening** Phase (see Sections 9.1.2. and 9.7.). ~~Note that the sponsor's tissue-based assay (archival or recently collected) may also be used to determine eligibility (see Section 9.7 for full details).~~ **Results obtained from the sponsor-validated assays from other Janssen-sponsored trials can be used to enter screening for this trial. Subjects who are positive for germline pathogenic BRCA1 or BRCA2 mutations will be allowed to be screened and enter the treatment phase based on local test results (blood or saliva) and will be confirmed by the sponsor-validated assay retrospectively. Subjects who are positive for somatic pathogenic BRCA1 or BRCA2 mutations by local test results (blood, saliva, or tissue) must be confirmed as positive by the sponsor-validated assay during screening before being able to enter the treatment phase.** c. Prescreening AEs: AEs and serious AEs related to blood or recent tumor tissue collection procedures, as well as death from any cause, will be collected for 30 days after the procedures **for subjects who sign the prescreening consent**. d. Main study informed consent: ~~Only biomarker-positive subjects may sign the main study informed consent, which~~**Main study consent** must be signed prior to the conduct of any study-related procedures in the Screening Phase.

Applicable Section(s)	Description of Change(s)
9.1.2. Prescreening Phase for Biomarker Evaluation	Text revised to note that if the subject is biomarker-positive by the sponsor-validated blood- or tissue-based assay, then he is eligible to enter the Screening Phase. Subjects who are positive for pathogenic BRCA1 or BRCA2 mutations based on local test results (somatic or germline) can enter the Screening Phase.
9.1.3. Screening Phase	Criteria for screening and advancement to the treatment phase clarified as: • Subjects positive for germline pathogenic BRCA1 or BRAC2 mutations based on local test results (blood or saliva); • Subjects positive for somatic pathogenic BRCA1 or BRAC2 mutations (blood, saliva, or tissue) based on local results confirmed as positive by the sponsor-validated assay during screening.
9.7. Biomarkers; Table 5	Information on biomarker-positivity criteria (ie, genomic lesions required for positivity) was removed from text and Table 5, as the definitions for positivity may evolve. Information on the method of histone deacetylase 2 gene (HDAC2) detection was also removed.
9.7.1. Evaluations	New subsections on tissue analysis and saliva testing were added as shown below: **9.7.1.1. Tumor tissue (either archival or recently collected) should be obtained to evaluate DRD status, and may also be used to identify markers associated with disease evolution, immune context, or response to study drugs. Tissue samples collected at screening may be used for concordance and bridging studies for the development of the assay. Furthermore, tumor tissue may be assessed for RNA signatures predictive of response to niraparib.** **9.7.1.5. Testing via a saliva sample may be collected to evaluate for germline mutations. Subjects will be permitted to be screened and enter the treatment phase if positive for BRCA1 or BRCA2 germline pathogenic mutations.**
11.3. Efficacy Analyses	The following text was added: **Anti-tumor activity, such as PSA response, CTC conversion, composite response rate, will be analyzed based on subgroups of the enrolled population of biallelic, monoallelic, and indeterminant (local test results only) biomarker status. Additional details will be provided in the SAP.**
11.6. Biomarker Analyses	Text was updated as follows (deletions appear in overstrike, new text in bold): The concordance of DNA-repair anomalies in genes ~~between~~ **among** tumor DNA and plasma ctDNA **results** ~~will~~ **may** be evaluated. ~~Analysis of biallelic loss in comparison to monoallelic mutation calling will be performed to determine if monoallelic mutation calling can be a proxy for biallelic loss.~~
Rationale: To align guidance on the use of niraparib with selected concomitant medications.	
1.2. Summary of Available Nonclinical and Clinical Data	Preclinical information on induction was updated.
8.2. Restricted Concomitant Medications	Text revised to qualify niraparib as a weak inducer of cytochrome P450 (CYP)1A2 in vitro, and to remove reference to P-glycoprotein (P-gp) inhibitors; further clarification was added regarding the concomitant use of niraparib with medications that are sensitive or moderately sensitive substrates of CYP1A2.
Attachment 5 Substrates of CYP1A2	The title of Attachment 5 was revised, and the list of CYP1A2 substrates and P-gP inhibitors removed and replaced with links to relevant references.

Applicable Section(s)	Description of Change(s)
Rationale: The noted conditions will be reported as part of the time to symptomatic skeletal events endpoint.	
Attachment 6 Anticipated Events	Deletion of the disease-specific events of pathological fracture, spinal cord compression, and cauda equine syndrome.
Rationale: Detail regarding specific blood collection tools was removed.	
9.7.1.2. Circulating Tumor Cells; 9.7.1.3. Whole Blood for RNA	Text describing the type of tube used for blood collection was deleted.
9.7.1.4. Circulating Tumor DNA	Minor edits were made to address the use of plasma samples and assay development.
Rationale: Information added to note where follow-up measures will be documented, and to clarify the local regulations regarding contact if the subject withdraws consent.	
10.2. Withdrawal from the Study	Text was updated as follows (bold text indicates new text): The measures taken to follow up must be documented **in the subjects' source documents**. If the subject withdraws consent for all study-related procedures, then no further contact is permitted by the investigator or the sponsor**, except as permitted by local regulations**.
Rationale: Minor changes, corrections, and errors were addressed throughout the protocol.	
17.11. Use of Information and Publication	Minor changes made as applicable in alignment with current protocol template.
Throughout the protocol	The term "patient" was revised to"subject" as appropriate. Minor grammatical, formatting, abbreviations, or spelling changes were made.

Amendment 6 (20 June 2019)

The overall reason for the amendment: is to modify and clarify the protocol's inclusion and exclusion criteria to align with current clinical practice for the treatment of patients with metastatic prostate cancer based on protocol steering committee feedback and to reflect the characteristics of the third line mCRPC population.

Applicable Section(s)	Description of Change(s)
Rationale: The protocol inclusion and exclusion criteria were revised to reflect the characteristics of the third line metastatic castration-resistant prostate cancer (mCRPC) population and to align with current clinical practice.	

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of Study Design and Subject Population); 3. Study Design; 4. Subject Population; 4.2. Inclusion Criteria; 9.1.2. Prescreening Phase for Biomarker Evaluation	Prior to this amendment, potential subjects were required to progress on a taxane-based chemotherapy, and AR-targeted therapy, both in mCRPC. In current clinical practice, based upon the CHAARTED and STAMPEDE data, taxane-based therapy is now given in the metastatic castration-sensitive prostate cancer (mCSPC) setting, such that resistance or intolerance to chemotherapy could have occurred in the mCSPC setting and rechallenge in the mCRPC setting would be of no benefit. Lavaud et al. observed those patients who received docetaxel rechallenge when they developed mCRPC have limited benefit from this treatment, as assessed by a PSA decline ≥50% obtained only in 14% of the patients in first- or second-line treatment.[14] Therefore, this criterion has been amended, and potential subjects now need to have received AR-targeted therapy and taxane-based chemotherapy with evidence of disease progression, or discontinued taxane-based chemotherapy due to an adverse event, in either mCSPC or mCRPC. As the current inclusion requirements continue to require at least one prior taxane and progression on a prior AR-targeted agent and have mCRPC disease, the study population remains unchanged by recruiting subjects who have received 2 lines of therapy, with the protocol therapy comprising the third line and the overall benefit-risk remains unchanged. This change was noted in Inclusion Criterion 5, Synopsis, and Sections 3, 4, and 9.1.2.
4.1. Prescreening Eligibility Criteria; 9.1.2. Prescreening Phase for Biomarker Evaluation	Prescreening Criterion 2 was edited to remove 'if feasible' as a qualifier for a potential subject's willingness to provide a tumor tissue sample, in order to highlight the importance of this sample. This change was also made in Section 9.1.2.
4.2. Inclusion Criteria	Inclusion Criterion 6 was edited to improve readability and implementation. Inclusion Criterion 14e was edited to correct the units used to report creatinine clearance.
4.3. Exclusion Criteria	Exclusion Criterion 15 was amended to decrease the minimum number of days required between a transfusion or receipt of hematopoietic growth factors and Cycle 1 Day 1 from 30 days to 14 days. No minimum number of days are now required prior to Cycle 1 Day 1 for receipt of an investigational agent for prostate cancer or major surgery.
Rationale: Text in the protocol was updated to reflect that a sponsor-validated blood- and tissue-based biomarker assay to detect biallelic DNA-repair anomalies is now available.	
Synopsis (Objectives, Endpoints/Assessments, and Hypothesis); Synopsis (Overview of Study Design); Time and Events Schedule; 2.1. Objectives and Endpoints/Assessments; 3. Study Design; 9.1.2. Prescreening Phase for Biomarker Evaluation; 9.7. Biomarkers; 11.1. Analysis Populations	Text in the protocol has been updated to reflect that a sponsor-validated blood- and tissue-based biomarker assay to detect biallelic DNA-repair anomalies is now available. As a result, the ITT Population is now defined as all subjects with biallelic DNA-repair anomalies as determined by a sponsor-validated blood- or tissue-based assay.
4.1. Prescreening Eligibility Criteria	For Criterion 2, 'using a sponsor-validated assay' was added to describe the method needed for determination of DNA-repair anomalies.

Applicable Section(s)	Description of Change(s)
Rationale: Serial PK sampling assessment on a subset of subjects has been removed from the protocol. The PK of niraparib monotherapy has been adequately characterized; therefore, only sparse PK sampling is required for this study.	
Synopsis (Pharmacokinetic Evaluations and Pharmacokinetics and Exposure-Response); Time and Events Schedule; 9.1.1. Overview; 9.3.1 Sample Collection and Handling; 9.3.3. Pharmacokinetic Parameters; 11.4. Pharmacokinetic Analyses	Text describing serial PK sampling was removed from the protocol.
Rationale: Clarification was added that the confirmation scan should occur 4 weeks after the first documentation of objective response for soft tissue disease (with the allowance of a 2-week window). This schedule is consistent with the current protocol attachments that describe RECIST 1.1.	
Time and Events Schedule; 9.2.2. Endpoints Criteria	The time of the confirmation scan was clarified to be 4 weeks after the first documentation of objective response for soft tissue disease (with the allowance of a 2-week window). The schedule for subsequent scans will be based upon Cycle 1 Day 1, and the confirmation scan will satisfy the scan requirements for the next occurring timepoint per the Time and Events Schedule.
Rationale: Minor changes, corrections, and errors were addressed throughout the protocol.	
Synopsis (Overview of Study Design); 3. Study Design	For consistency, 'approximately' was added before the number of subjects planned to be enrolled with BRCA1 or BRCA2 DNA-repair anomalies and the number of subjects planned to be enrolled with ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2 DNA-repair anomalies.
2.1. Objectives and Endpoints/Assessment	Text for the exploratory endpoint 'time to unequivocal clinical progression' was edited for accuracy to include the word 'clinical'.
6.2.1. Non-hematologic toxicities	The title of Table 2 was edited by adding 'drug-related' in order to align with the text in Section 6.2.1.
9.1.3. Screening Phase	Removed that a subject requires sponsor approval and agreement to be rescreened. Rescreening is solely at the discretion of the investigator.
9.1.6. Follow-up Phase	Clarified that regular imaging should be collected from the EoT visit until radiographic progression only for subjects who have not started a subsequent treatment for prostate cancer or withdrawn consent.
9.7. Biomarkers	Table 5 has been modified to provide further details on the different criteria used in the blood- versus tissue-based assays.
Attachment 5	In the list of examples of CYP1A2 substrates, (R)warfarin was changed to warfarin.
Investigator Agreement Page	The name of the responsible medical officer has been updated from NamPhuong Tran, MD to Shinta Cheng, MD.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 5 (30 November 2018)

The overall reason for the amendment: Based on the updated safety information of niraparib with more subjects exposed to drug and to be consistent with clinical practice of physicians, changes were made to inclusion/exclusion criteria and other study-related procedures throughout the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Changes were made due to anticipated availability of a tissue-based assay.	
Synopsis, Objectives, Endpoints/Assessments, And Hypothesis, Overview of Study Design; Time and Events Schedule, footnote 'b'; 9.1.2. Prescreening Phase for Biomarker Evaluation; 9.7. Biomarkers	Throughout the protocol, the subject enrollment criteria to allow for enrollment based on tissue determination of DNA-repair anomalies once an algorithm that can distinguish biallelic from monoallelic DNA-repair anomalies is available was included.
Rationale: The anticoagulation criterion was removed as additional experience with niraparib has not suggested increased risk of bleeding if subjects are on anticoagulation agents.	
4.3. Exclusion Criteria (Criterion 16)	Following text was deleted: Subjects who are currently taking anticoagulation therapy (eg, warfarin, enoxaparin, dabigatran, rivaroxaban).
Rationale: Based on the updated safety information of niraparib, QT interval prolongation was not identified as a risk.	
4.3. Exclusion Criteria (Criterion 11)	Following text was deleted: Corrected QT interval by the Fridericia correction formula (QTcF) on the screening ECG >450 msec.
Rationale: Revision and modifications were made for clarity and consistency with the updated safety information of niraparib.	
Time and Events Schedule	Timepoints of assessment of vital signs, blood pressure and physical examination were updated and frequency was reduced.
4.1. Prescreening Eligibility Criteria, Criterion 3	Text was updated as follows (bold text indicates new text): Must ~~have documented evidence of disease progression while~~ **be** on **or after** second-line of treatment for mCRPC.
4.2. Inclusion Criteria (Criterion 5)	Text was updated as follows (bold text indicates new text): **Received at** least 1 line of taxane-based chemotherapy for the treatment of **mCRPC** with documented evidence of disease progression **prior to enrollment** ~~while on therapy or within 3 months after discontinuation of therapy in the castrate-resistant setting~~.

Applicable Section(s)	Description of Change(s)
4.2. Inclusion Criteria (Criterion 6)	Text was updated as follows (bold text indicates new text): **Received at** least 1 line of AR-targeted therapy (eg, abiraterone acetate plus prednisone, enzalutamide, apalutamide) for **mCRPC** with documented evidence of disease progression **prior to enrollment**~~while on therapy or within 3 months after discontinuation of therapy in the castrate-resistant setting.~~
4.2. Inclusion Criteria (Criterion 14)	Criteria for certain screening laboratory parameters were updated as follows (bold text indicates new text): e. ~~Serum creatinine ≤1.5 x upper limit of normal (ULN), or a calculated c~~**C**reatinine clearance ≥~~6~~**3**0 mL/min/1.73 m^2 ~~using the Cockcroft-Gault equation~~. ~~f Serum potassium ≥3.5 mmol/L~~ g Serum total bilirubin ≤1.5 × ULN or direct bilirubin ≤1 x ULN (Note: in subjects with Gilbert's syndrome, ~~if total bilirubin is >1.5 x ULN, measure direct and indirect bilirubin, and~~ if direct bilirubin is ≤1.5 x ULN, subject may be eligible) h Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x ULN ~~or AST and ALT ≤5 x ULN in the presence of liver metastases~~
4.3. Exclusion Criteria (Criterion 4)	Text was updated as follows: ~~Known~~ **S**ymptomatic or impending cord compression, except if subject has received definitive treatment for this and demonstrates evidence of clinically stable disease.
4.3. Exclusion Criteria (Criterion 5)	Text was updated as follows: ~~Known~~ **S**ymptomatic ~~uncontrolled~~ brain ~~or leptomeningeal~~ metastases ~~(controlled is defined as CNS disease which has undergone treatment [eg, radiation or surgery] at least 15 days prior to Cycle 1 Day 1)~~
4.3. Exclusion Criteria (Criterion 10)	Text was updated as follows (bold text indicates new text): Prior **palliative** radiotherapy ≤~~7~~**15** days prior to Cycle 1 Day 1**. Radiotherapy given >7 days prior to Cycle 1 Day 1 is permitted as long as any AEs associated with radiotherapy have resolved to Grade 1 or baseline.**~~, with the exception of a single fraction of radiotherapy for the purposes of palliation, which is permitted.~~
4.3. Exclusion Criteria (Criterion 17)	Text was updated as follows (bold text indicates new text): Subjects with uncontrolled (persistent) hypertension ~~Grade ≥3 (ie, Stage 2 hypertension [systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg]) confirmed by multiple readings~~ **defined as systolic blood pressure [BP] ≥160 mm Hg or diastolic BP ≥100 mm Hg) despite medical management.**
Table 5. Biomarker Panel and Criteria for Positivity	Control genes (AR, TP53, and CDK2NA) and the footnotes with related cross references in table were deleted from the table.
9.2.2. Endpoints Criteria	Text for bone scan progression was updated and clarified. The text on duration of tumor response was updated to make it consistent with the secondary objective of study. Text was updated as follows (bold text indicates new text): The duration of tumor response will be assessed from the first time of observed CR/PR to the date of radiographic progression ~~(as per PCWG3)~~, **unequivocal clinical progression, or death, whichever occurs first**.

Applicable Section(s)	Description of Change(s)
9.9. Safety (Adverse Events)	Text was updated as follows: ~~Potential~~ AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study ~~and investigators will determine if the events are recorded as AEs~~. AEs will be followed by the investigator as specified in Section 12, Adverse Event Reporting.
10.1. Discontinuation of Study Treatment	• The criterion of need for chronic opioid analgesics under unequivocal clinical progression was removed. • The criterion of use of external beam radiation therapy to relieve skeletal symptoms under tumor progression was updated to "Radiation therapy" • The criterion of the need for tumor-related orthopedic surgical intervention under tumor progression was updated to "Surgical interventions for complications due to tumor progression" • "Diagnosis of MDS/AML" was newly added under criteria for discontinuation of study treatment. • Text was added indicating that "**Palliative radiation therapy for bone pain may not require a subject to be discontinued from treatment, after discussion with the medical monitor.**"
14.4. Preparation, Handling, and Storage	Following sentence was added: "Caregivers should handle niraparib with protection (eg, gloves)"
Rationale: Based on the updated safety information of niraparib, the requirements for ECGs have been modified.	
Time and Events Schedule, including Footnote 'g'; 9.9. Safety (Electrocardiogram [ECG])	Specified that triplicate ECGs are not required. A standard 12-lead ECG recording will be used in this study. Footnote 'g' was updated as follows (bold text indicates new text): **Standard 12-lead ECGs** will be performed at screening, at every cycle through Cycle 7, **at every 3 cycles thereafter**, at the EoT visit, **and as clinically indicated.** The following text was deleted: Triplicate ECGs must be performed at approximately the same time of day (±3 hours) at each cycle
Rationale: Benefit-risk assessment for niraparib monotherapy was added to supplement the protocol.	
1.3. Benefit/Risk Assessment	Benefit-Risk Assessment section added.
Rationale: Dose modifications and management of drug toxicities (hematologic and non-hematologic) were updated to reflect the clinical practice of physicians.	
6.2. Dose Modification and Management of Toxicity	It was clarified that any re-escalation of the reduced dose to a full starting dose should be discussed in advance with Sponsor's medical monitor.
6.2.1. Non-hematologic Toxicities	Text was updated to clarify the dose modifications in drug-related Grade 3 or higher toxicities.
6.2.1.1. Hepatic Toxicities	Since hepatic toxicities are known potential side effect of niraparib, new section was added to clarify the dose modification criteria for hepatic toxicities. New Table 3. Dose Modification Criteria for AST/ALT/Bilirubin Abnormalities for Niraparib added.

Applicable Section(s)	Description of Change(s)
6.2.2. Hematologic Toxicities	New text was added to clarify that the site should contact the Sponsor for discussion and consider discontinuation of niraparib if hematologic toxicity has not recovered to Grade 1 or baseline after 28 days of dose interruption or a diagnosis of MDS/AML is confirmed by a hematologist.
6.3. Treatment Interruptions for Planned Procedures	New section added to clarify the duration of interruption of nirparib dose for planned procedures that require hospitalization.
Table 4, Dose Modification/Reductions for Hematologic Toxicity (Platelet Count and White Blood Cell Count)	"White Blood Cell" was replaced with "Neutrophil" in the table header.
Rationale: To be consistent with Patient-reported Outcome (PRO) completion guidelines.	
Time and Events Schedule; 9.1.1. Overview	Patient-reported Outcomes should be performed first prior to any study-related procedures if multiple assessments are planned at the same timepoint. New footnote "i" was added in Time and Events Schedule.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 4 (20 March 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary reason for the amendment: is to improve the subject selection criteria based on using an enhanced biomarker assay and the corresponding statistical analysis plan, to remove Holter monitoring, and other minor changes throughout the protocol.

The rationale for and description of the changes are listed below, and representative revisions are sometimes provided; when revisions are provided verbatim, bold font denotes new text and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Rationale: Internal sponsor analyses on subjects enrolled in this study prior to 07 December 2017 showed that subjects with measurable mCRPC who have biallelic DNA-repair anomalies in BRCA1 or BRCA2 genes potentially have greater clinical benefit from treatment with niraparib. Therefore, the primary endpoint analysis of the study was amended to evaluate the response of these subjects. A secondary endpoint analysis to evaluate the response of subjects with other DNA-repair anomalies (in ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2) was added. In addition, a futility analysis for subjects with measurable mCRPC who have biallelic DNA-repair anomalies in ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2 was implemented to ensure that recruitment of these subjects is not continued if an adequate response is not initially observed.	

Applicable Section(s)	Description of Change(s)
Synopsis (Objectives, Endpoints/Assessments, and Hypothesis); Synopsis (Overview of Study Design); 2.1. Objectives and Endpoints/Assessments; 3. Study Design	Updates were made to the patient population, the number of subjects enrolled in each population, and to the primary and secondary objectives and endpoints of the study.
Table 4	Revisions and clarifications were made to the table and footnotes, and a new footnote was added.
Synopsis (Statistical Methods); 11.2. Sample Size Determination	Descriptions of primary and secondary objectives with objective response rate (ORR) endpoint were revised based on updates to the patient population. In addition to the interim efficacy analysis for the primary endpoint (as in the original protocol), a futility analysis for ORR based on Simon's two-stage design was added for the secondary objective in subjects with measurable mCRPC who have biallelic DNA-repair anomalies in ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2.
11.1. Analysis Population	ITT Population: All subjects who have biallelic DNA-repair gene anomalies (as determined by the sponsor's **required** blood-based assay) **and were enrolled after 07 December 2017**. This population will be used for efficacy analyses.
11.3. Efficacy Analyses	~~The primary endpoint,~~ ORR **in subjects with measurable mCRPC and DNA-repair anomalies in BRCA1 or BRCA2 and ORR in subjects with measurable mCRPC and DNA-repair anomalies in ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2**, as defined in Section 2.1, will be calculated, and its 2-sided 95% exact CI will also be presented. The final analysis for ORR **in subjects with measurable mCRPC and DNA-repair anomalies in BRCA1 or BRCA2** will be performed approximately 6 months after the last subject with measurable disease **and DNA-repair anomalies in BRCA1 or BRCA2** receives his first dose of study medication.
Rationale: Two more study visits were added to Cycle 1, to enhance safety monitoring.	
Time and Events Schedule	Two columns were added to Cycle 1 (for Day 8 and Day 22 timepoints), to provide weekly monitoring during the first cycle.
Rationale: The requirement for Holter monitoring was removed, since triplicate ECGs are required on Day 1 of every cycle, and no concern for QT prolongation has been observed in other studies.	
Synopsis (Pharmacokinetic Evaluations); Time and Events Schedule, including Footnotes g and k; 9.3.1. Sample Collection and Handling; 9.9. Safety (Electrocardiogram [ECG])	The requirement for Holter monitoring was removed. Specified that triplicate ECGs are required.
Rationale: Revisions and modifications were made throughout the protocol to increase clarity and consistency, to update the protocol based on revisions made during this amendment, or to correct omissions and errors.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Applicable Section(s)	Description of Change(s)
Throughout the protocol	"3 months" was revised to "12 weeks" (or "12 weeks" was added in parenthesis after "3 months"), "6 months" was revised to "24 weeks", "sponsor's blood-based assay" was revised to "sponsor's required blood-based assay".
Time and Events Schedule; 9.1.3. Screening Phase	The Screening Phase was reduced from 35 days to 28 days in order to allow subjects to receive the Cycle 1 Day 1 dose sooner.
Abbreviations	Abbreviations and definitions were added.
4.1. Prescreening Eligibility Criteria	Criterion 4 was deleted. Details will be provided in the laboratory manual.
4.2. Inclusion Criteria (Criterion 8)	a. PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination (per Prostate Cancer Working Group 3 [PCWG3] criteria).[19] The PSA level at the screening visit should be ≥~~2~~ **1** µg/L (~~2~~ **1** ng/mL).
4.2. Inclusion Criteria (Criterion 14)	h. Aspartate aminotransferase (AST) ~~or~~ **and** alanine aminotransferase (ALT) ≤3.0 x ULN or **AST and ALT** ≤5 x ULN in the presence of liver metastases i. CTC count of ≥1 cells/7.5 mL blood **(required only for patients with non-measurable soft tissue disease by RECIST 1.1)**
6.2. Dose Modification and Management of Toxicity	For procedures while on treatment, dose interruption of up to 28 days is allowed. **Dose interruptions of more than 28 days must be discussed in advance with the sponsor's medical monitor.**
6.2.1. Non-hematologic Toxicities	This section was revised for accuracy, and repetitions were removed.
6.2.2. Hematologic Toxicities	Repetitions were removed based on text added to Section 6.2. Management of anemia was amended to align with institutional standards of care. The order of dose reductions for Grade ≥3 hematologic toxicity in Table 3 was revised to start with the highest dose, and a note was modified as shown below. • Weekly monitoring and/or interruption are not required if ~~at baseline grade, eg, subject with baseline Hgb 9.1 (grade 2 anemia) does not need to be monitored weekly for grade 1 or 2 anemia~~ **values return to baseline levels**.
6.3. Treatment Continuation Criteria for the First Day of a New Cycle	Revisions were made to treatment continuation criteria for the first day of a new cycle.
8. Concomitant Therapy	Concurrent enrollment in another **interventional** investigational drug or device study is prohibited during the Treatment Phase.
9.1.2. Prescreening Phase for Biomarker Evaluation	The Prescreening Phase may occur **at** any time prior to the Screening Phase, including ~~during~~ **while** the ~~subject's~~ **subject is on a** second-line of therapy **provided the subject is demonstrating signs of progression (eg, rising PSA or radiographic progression)**. If no tumor tissue is available, then the subject may ~~agree~~ **be asked** to have a new tumor tissue sample collected**, if reasonable**. For consistency for changes in Section 4.1, the following sentence was deleted: "Subjects may be rescreened once for biomarker-positivity during the Prescreening Phase for the reasons described in Section 4.1, Criterion 4."

Applicable Section(s)	Description of Change(s)
9.7. Biomarkers	To be eligible for the study, subjects must be confirmed biomarker-positive by the sponsor's **required** blood-based assay. To ensure that all subjects have the same biomarker data available for analysis (~~ie~~ **eg**, for concordance and bridging studies), blood samples will be collected and analyzed from all subjects who sign the prescreening ICF. **Tissue samples will also be collected for additional biomarker research.** Clarifications and revisions were made to Table 4 and its footnotes, and a new footnote was added.
10.2. Withdrawal from the Study	This can be done by telephone ~~or by~~ chart review **or by public record search if permissible by local regulations**.
10.3. Withdrawal From the Use of Samples in Future Research	The subject may withdraw consent for use of samples for **future** research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research).
11.11. Safety Analyses (Clinical Laboratory Tests)	Clinical laboratory test results will be collected from screening through ~~30 days after last dose of study drug~~ **the EoT visit**.
12.3.4. Disease Progression and Death	Fatal events (regardless of relationship to study drug) should be reported as SAEs for subjects until 30 days after ~~EoT~~ **the last dose of study drug**. **Fatal events occurring after that 30-day period after the last dose of study drug will not be reported as SAEs and will be captured on the designated case report form for survival.** Death is an outcome of an AE and not an AE itself. All reports of death within 30 days ~~of EoT~~ **after the last dose of study drug** should include an AE term for the cause of death (if known). ~~Fatal events occurring after that 30-day EoT visit will not be reported as SAEs and will be captured on the designated case report form for survival.~~
15. Study-Specific Materials	Revisions were made to the supplies provided to the investigator.
16.2.3. Informed Consent	~~The physician may also recontact the subject for the purpose of obtaining consent to collect information about his survival status.~~
References	A new reference was added. The edition number and year were deleted from the citation for the Investigator's Brochure.

<u>Amendment 3</u> (4 October 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary reason for the amendment: is to include additional cardiac monitoring to better understand the cardiovascular effect of niraparib monotherapy in the prostate cancer population. This additional safety monitoring is precautionary only and is not indicative of a known cardiac signal for niraparib. An ITT Population was also added to allow for all subjects with biallelic DNA-repair anomalies to be analyzed separately for efficacy. Other minor changes (ie, removal of pharmacodynamics sampling and updates to the inclusion/exclusion criteria) are also included in this amendment.

Applicable Section(s)	Description of Change(s)
Rationale: Additional 12-lead electrocardiogram (ECG) Holter monitoring (24 hours) was added for subjects who are undergoing serial PK sampling for analysis of QT/QTc in relation to plasma concentrations of niraparib and M1.	

Applicable Section(s)	Description of Change(s)
Synopsis; Time and Events Schedule; 9.9. Safety	12-lead ECG Holter monitoring was added for subjects who are selected for serial PK sampling.
9.3.1. Sample Collection and Handling	A reference to Holter monitoring for subjects who undergo serial PK sampling was added.
Rationale: Subjects with biallelic DNA-repair anomalies are expected to have better clinical response outcomes than those subjects with monoallelic DNA-repair anomalies. Therefore, the sponsor intends to analyze these subjects separately for efficacy. To that end, an ITT Population comprising subjects who have biallelic DNA-repair gene anomalies (as determined by the sponsor's blood-based assay) was added.	
11.1. Analysis Populations	The Treated Population was amended to Enrolled Population to allow for all subjects enrolled in the study to be analyzed. An ITT Population was added to allow for all subjects with biallelic DNA-repair anomalies to be analyzed separately for efficacy.
Rationale: Pharmacodynamics sampling (ie, whole blood for isolation of PBMCs) was removed from the protocol. All blood samples collected to date are unusable due to contamination with high levels of poly-adenosine diphosphate [ADP]-ribose (PAR), likely from red blood cell lysis. Furthermore, preliminary data suggest that >50% of this subject population would yield PBMC counts below the threshold needed to exceed the PAR lower limit of detection.	
Synopsis: Pharmacodynamic Evaluations; Time and Events Schedule; 9.1.1. Overview; 9.1.4. Treatment Phase; 9.5. Pharmacodynamics; 9.6. Pharmacokinetic/ Pharmacodynamic Evaluations; 11.5 Pharmacodynamic Analyses; 11.8. Pharmacokinetic/ Pharmacodynamic Analyses	Pharmacodynamics sampling and analyses were removed.
2.1. Objectives and Endpoints/Assessments	The exploratory endpoint to quantify PAR levels in PBMCs was removed.
Rationale: Minor amendments	
Time and Events Schedule; 9.1.4. Treatment Phase; 9.1.5. End-of-Treatment Visit; 12.3.4; Disease Progression and Death	The definition of End-of-Treatment visit was amended to clarify that the visit should occur 30 (±5) days after the last dose of study drug or 30 (±5) days after the end of study drug interruption period.
Time and Events Schedule	The footnote for blood pressure monitoring was removed. Blood pressure will be measured at every cycle until the End-of-Treatment visit; no cap on the number of cycles will be implemented.
Synopsis; Time and Events Schedule; 9.2.1. Evaluations; 9.2.2. Endpoints Criteria	The instructions regarding tumor measurements and collection of imaging scans was updated to clarify different procedures for soft tissue response versus bone scan progression. Reference to the protocol body for additional details was added in the Time and Events Schedule footnote.

Applicable Section(s)	Description of Change(s)
Synopsis; 2.1. Objectives and Endpoints/Assessments	Clarified that the endpoint for CTC response should be performed for subjects who have baseline CTC >0.
Synopsis; 3. Study Design; 4. Subject Population	Clarified that subjects should have progressed on or after at least 1 line of taxane-based chemotherapy and at least 1 line of AR-targeted therapy (eg, abiraterone acetate plus prednisone, enzalutamide, apalutamide).
4.1. Prescreening Eligibility Criteria	Criterion 2 was updated to state that tumor tissue samples should be collected "if feasible". This is to allow subjects who may not be able to provide a tumor tissue sample to enter the study if a blood sample is available. Criterion 3 was amended to ensure subjects have documented evidence of disease progression while on second-line of therapy. Criterion 4 was updated to clarify when subjects could be rescreened for biomarker-positivity.
4.2. Inclusion Criteria	Minor amendments were made to inclusion criteria 5 and 6 to clarify the timing of discontinuation for prior taxane-based chemotherapies or AR-targeted therapies. Criterion 7 was updated to remove the requirement for tumor tissue to be biomarker-positive, given that subjects may be biomarker-positive based on the blood-based assay.
4.3 Exclusion Criteria	Criterion 12 was deleted. Medications thought to cause QT prolongation were instead added to Section 8.2 Restricted Concomitant Medications. Criterion 16 was added to exclude subjects who are taking anticoagulation therapy. Criterion 17 was added to exclude subjects with uncontrolled Grade ≥3 hypertension.
6.2.1. Non-hematologic Toxicities	Updated to include instructions for when subjects should be referred to a cardiologist and to allow for treatment interruption of Grade 1 and 2 non-hematologic toxicities at the discretion of the investigator. Clarified that treatment-related toxicities of Grade 3 or 4 require a dose reduction.
6.2.2. Hematologic Toxicities	Instructions for dose modifications/reductions for hematologic toxicities were updated to reflect toxicity grades, rather than specific laboratory values.
6.3. Cycle 1 Day 1 and Treatment Continuation Criteria	New section added to provide criteria for allowing subjects to be retreated with study drug.
8.1. Prohibited Concomitant Medications; 8.2. Restricted Concomitant Medications	Medications thought to cause QT prolongation or torsades de pointes were changed from prohibited to restricted medications.
9.1.2. Prescreening Phase for Biomarker Evaluation	Modified to allow for subjects who may not be able to provide a tumor tissue sample.
9.2.1. Evaluations;	Information regarding collection of scans to determine objective response and radiographic progression was moved to Section 9.2.2.
9.2.2. Endpoints Criteria	Information regarding collection of scans to determine objective response and radiographic progression was added to this section.
9.7. Biomarkers	The requirement to have biomarker-positivity determined by tumor tissue was removed.

Applicable Section(s)	Description of Change(s)
	The positivity criteria for the biomarker assay was updated to reflect the current blood-based assay.
10.1. Discontinuation of Study Treatment	Updated to remove discontinuation due to drug-induced liver injury, as the information conflicted with toxicity management guidance provided in Section 6.
	Updated QTc discontinuation criteria to state "clinically significant QTcF >500 msec or QTc prolongation >60 ms above baseline"
11.2 Sample Size Determination	The anticipated enrollment duration was removed.
11.3. Efficacy Analyses	Updated to reflect that the primary efficacy analysis would be performed using the ITT Population.
11.10. Interim Analysis	Removed statement that no formal interim analysis would be performed. Interim analyses will be described in the statistical analysis plan.
12.3.1. All Adverse Events	Added the collection of related serious adverse events and deaths from any cause during the Prescreening Phase.
Attachment 1	Removed from protocol for copyright reasons.
Attachment 4	Removed from protocol, as a more comprehensive list of medications thought to cause QT prolongation was included in reference 17.
Attachment 6	Updated list of anticipated events to be disease-specific.
Rationale: Minor errors were noted and corrected	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (25 January 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to address feedback from a Type C Meeting with FDA held on 19 October 2016, as well as feedback from other health authorities.

Applicable Section(s)	Description of Change(s)
Rationale: The primary endpoint of the study was amended to comply with feedback from health authorities. The primary endpoint was changed from a composite endpoint to objective response rate (ORR). With this change, the subject population for the primary analysis will include only subjects with measurable disease. Subjects with non-measurable disease will still be included in the study to increase the size of the safety database and assess the activity of niraparib in this population.	
Synopsis; 2.1. Objectives and Endpoints/Assessments	The primary endpoint is changed from a composite endpoint to an endpoint of objective response rate (ORR) in subjects with measurable disease.
	Given that circulating tumor cell (CTC) response was no longer included in the primary endpoint, an additional secondary endpoint to measure CTC response was added. The exploratory endpoint to evaluate CTC counts was also updated based on the new secondary endpoint.
	The original composite primary endpoint was changed to be an exploratory endpoint.

Applicable Section(s)	Description of Change(s)
	An additional exploratory endpoint of time to unequivocal progression was included.
Synopsis; 2.2. Hypothesis	The hypothesis was amended to reflect the new primary endpoint and corresponding statistical assumptions.
Synopsis; 3. Study Design	The study design was updated to amend the number of subjects to be included in the study, and to be aligned with Section 11.2 Sample Size Determination. Other administrative changes were made.
Synopsis; Time and Events Schedule; 9.1.4. Treatment Phase; 9.2.1. Evaluations	The new primary endpoint of ORR requires confirmation of response; therefore, details of collection and review of imaging scans were updated and the time window for collection was changed from ±7 days to ±3 days.
Synopsis; 11.2. Sample Size Determination	The sample size calculations were amended to reflect the new primary endpoint of ORR. Sample size justification for subjects with non-measurable disease based on CTC RR was also added.
Synopsis; 11.3 Efficacy Analyses	The efficacy analyses were amended to reflect the new primary endpoint of ORR. In addition, analysis of CTC RR was added to address the additional secondary endpoint of CTC response.
Rationale: To comply with US FDA recommendations	
Time and Events Schedule	Safety testing at Cycle 2 Day 15 was added to ensure the safety of subjects early in the study, as recommended by US FDA.
Rationale: To collect additional PK samples to characterize exposure of niraparib and its metabolite M1.	
Synopsis; Time and Events Schedule; 9.3. Pharmacokinetics; 11.4. Pharmacokinetic Analyses	Additional serial PK samples were added in a subset of subjects at selected sites. Clarification was added that sparse PK sampling will be collected in all subjects.
9.1.1. Overview	The maximum volume of blood drawn at any visit was amended from 70 mL to 80 mL based on the additional PK collections required in a subset of subjects.
2.1. Objectives and Endpoints/Assessments	Additional exploratory endpoints were included to evaluate the steady-state PK of niraparib and its metabolite M1 in a subset of subjects.
Rationale: To clarify the subject population to be included in the study based on health authority and investigator feedback	
4.1. Prescreening Eligibility Criteria	Criterion 3 was added to allow subjects who are on second-line therapy to enter the Prescreening Phase, although they will not be eligible to enter the Screening Phase until they have progressed on their second-line of therapy. Criterion 4 was added to allow subjects who are biomarker-negative to be rescreened once, to determine if their tumor tissue was insufficient for analysis or to determine of their biomarker status changed over the course of their disease.
4.2. Inclusion Criteria	Criterion 4 was updated to clarify that prostate cancer of mixed histology is acceptable; however, subjects with the small cell pure phenotype of prostate cancer must be excluded from the study. Criterion 5 was updated to specify that subjects must have documented evidence of disease progression on previous taxane-based chemotherapy. Criterion 6 was updated to specify that subjects must have documented evidence of disease progression on previous AR-targeted therapy.

Applicable Section(s)	Description of Change(s)
	Criterion 8 was updated to specify that PSA progression must be determined per PCWG3 guidelines and radiographic progression must be determined as per RECIST 1.1 (for soft tissue) or PCWG3 (for bone disease) criteria. Clear definitions of measurable and non-measurable disease were added. Criterion 14 was updated to amend platelet counts and serum albumin levels at screening. In addition, a criterion for CTC count was added (criterion 14.1.i) to define the permitted levels at screening.
4.3. Exclusion Criteria	Criterion 2 was updated to clarify that previous chemotherapy should only be an exclusion criterion if it was used for the treatment of prostate cancer. Criterion 11 was corrected to exclude subjects with QTcF on the screening ECG >450 msec, as per ICH E14: *The Clinical Evaluation of QT/QTc Interval prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* Criterion 15 was amended to remove zoledronic acid and denosumab as prohibited prior therapies.
Rationale: To ensure consistency with Investigator's Brochure	
Time and Events Schedule	Additional blood pressure measurements were added; blood pressure should now be measured at all study visits.
6.2.1. Non-hematologic toxicities	The time permitted for dose interruption was amended from 21 days to 28-days to reflect the Investigator's Brochure and to align with treatment cycles.
6.2.2. Hematologic Toxicities	Recommendations for dose modification/reductions for hematologic toxicity were updated to reflect the current Investigator's Brochure (version 6.0). Updates are captured in Table 4. The time permitted for dose interruption was amended from 21 days to 28-days to reflect the Investigator's Brochure and to align with treatment cycles.
9.9. Safety	Additional serum chemistry tests have been added and albumin will now be measured at all visits requiring laboratory testing (not just at screening). These new clinical laboratory tests were not added due to any new safety signals and are compliant with recommendations in Investigator Brochure version 5.
Attachment 6: Anticipated Events	Additional anticipated events were included to align with the Investigator's Brochure.
Rationale: To comply with feedback from US FDA regarding the evaluable biomarker population for efficacy and to simplify instructions for investigators.	
9.1.2. Prescreening Phase for Biomarker Evaluation	All subjects in the study are required to have tumor tissue and a blood sample collected for analysis of biomarkers. Details of how those samples will be analyzed and which assays will be used were condensed and were moved to Section 9.7 Biomarkers. New text was added to clarify that potential subjects can enter the Prescreening Phase if they are on second-line therapy.
Rationale: To clarify that imaging scans may be collected during follow-up from subjects who discontinue treatment for reasons other than radiographic progression.	
Time and Events Schedule; 9.1.6. Follow-up Phase	The sponsor intends to collect imaging scans from subjects who discontinue treatment for reasons other than radiographic progression, in order to determine radiographic progression-free survival, provided the subject does not withdraw consent for collection of images. Therefore, collection of imaging scans during the Follow-up Phase was clarified, including the collection window to be applied (ie, every 3 months ±2 weeks).

Applicable Section(s)	Description of Change(s)
Rationale: To clarify withdrawal from study categories and the testing procedures permitted based on the type of withdrawal.	
10.1. Discontinuation of Study Treatment	Additional categories for withdrawal from the study treatment were included and the procedures permitted for each category of withdrawal were clarified.
10.2. Withdrawal from the Study	Clarification was added for follow-up visits to allow for telephone or chart review. Clarification was also added regarding subjects who withdraw consent for all study-related procedures; these subjects must not be contacted by the investigator or the sponsor.
Rationale: Minor amendments	
Title Page	The study name "Galahad" was added.
Time and Events Schedule	Clarifications were added regarding the collection window for follow-up visits, the collection of related serious adverse events, the collection of symptomatic skeletal events, and the collection of patient-reported outcomes. Collection and review of imaging scans was also updated. In order to clarify when assessments occur after Cycle 7 (ie, from Cycle 8 onwards), an additional column was added for assessments that occur on every cycle. As a result, footnotes stipulating that study drug dispensation and treatment compliance are to be completed every cycle were deleted.
Time and Events Schedule; 9.5 Pharmacodynamics	Added text to allow the collection of PBMCs at select sites only, and for collection PBMCs to be discontinued at the sponsor's discretion, based on the data collected.
6.1. Study Drug Administration	Clarified that missed doses do not cause cycles to be delayed or restarted.
11.10. Interim Analysis; 16.1. Study-specific Design Considerations	Text describing a preliminary assessment of safety and efficacy in the first 30 subjects was removed. Information regarding this assessment will be included in the statistical analysis plan.
16.1. Study-specific Design Considerations	Amended to reflect the new primary endpoint and clarified that frequency of scanning is consistent with requirements to assess rPFS by PCWG3 criteria.
16.2.3. Informed Consent	Removed language regarding the process for informed consent when prior consent of a subject is not possible because this study will not enroll subjects who cannot give prior informed consent.
Attachment 2: Summary of RECIST Criteria Version 1.1 with Integration of PCWG3 for Evaluation of Response	Updated the definitions of best overall response based on PCWG3 criteria.
Attachment 4: Prohibited Medications That Could Potentially Cause QT Prolongation or Torsades de Pointes	Clarified that the table provided is not a complete list and that new medications may be considered as appropriate.
Investigator Agreement	Updated the sponsor's responsible Medical Officer.

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted and corrected	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (7 July 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to address feedback from FDA received 5 July 2016.

Applicable Section(s)	Description of Change(s)
Rationale: ECG monitoring at every cycle was added due to FDA concern regarding higher ECG abnormalities in the elderly population.	
Time and Events Schedule	ECG monitoring was added at every cycle.
9.9. Safety Evaluations	ECG monitoring procedures were clarified.
Rationale: FDA recommendation that toxicities which have not resolved within 21 days should undergo dose reduction or discontinuation.	
6.2.1. Non-hematologic Toxicities	Toxicities leading to dose modification should be resolved within 21 days, instead of 28 days.
Rationale: FDA recommendation that a hematologist must be consulted in the event of >1 transfusion or that did not recover to Grade 1 or less after 28 days.	
6.2.2. Hematologic Toxicities	The recommendation for subjects to see a hematologist was changed to a requirement in cases of hematologic toxicity that required >1 transfusion or that did not recover to Grade 1 or less after 28 days.
Rationale: FoundationOne® is the trademarked name for the commercial assay and cannot be used for the sponsor-approved test.	
9.1.2. Prescreening Phase	The FoundationOne® gene panel name was removed.

SYNOPSIS

A Phase 2 Efficacy and Safety Study of Niraparib in Men with Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies

Niraparib is an orally available, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, with activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases. Niraparib is being investigated for the treatment of ovarian, breast, and prostate tumors in subjects with DNA-repair anomalies.

OBJECTIVES, ENDPOINTS/ASSESSMENTS, AND HYPOTHESIS

Efficacy objectives will be evaluated for subjects who have either biallelic DNA-repair anomalies (BRCA or non-BRCA) as determined by a sponsor-validated blood- or tissue-based assay or germline pathogenic BRCA (BRCA1 or BRCA2) mutation.

Objectives	Endpoints/Assessments
Primary	
• To assess the efficacy of niraparib in subjects with measurable mCRPC and who have either biallelic DNA-repair anomalies in BRCA (BRCA1 or BRCA2) or germline BRCA	• Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with no evidence of bone progression according to the PCWG3 criteria
Secondary	
• To assess the efficacy of niraparib in subjects with measurable mCRPC and DNA-repair anomalies in biallelic non-BRCA (ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2)	• Objective response rate of soft tissue (visceral or nodal disease) as defined by RECIST 1.1 with no evidence of bone progression according to the PCWG3 criteria
• To assess the efficacy of niraparib in subjects with mCRPC and DNA-repair anomalies	• Circulating tumor cell (CTC) response defined as CTC=0 per 7.5 mL blood at 8 weeks post-baseline in subjects with baseline CTC >0
• To evaluate response outcomes of niraparib in subjects with mCRPC and DNA-repair anomalies	• OS: time from enrollment to death from any cause • As defined by PCWG3: – rPFS: time from enrollment to radiographic progression or death from any cause, whichever occurs first – Time to radiographic progression – Time to PSA progression – Time to symptomatic skeletal event (SSE)
• To evaluate the safety and tolerability of niraparib	• Incidence of adverse events • Clinical laboratory test results
• To evaluate duration of tumor response	• Duration of objective response: time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first

Abbreviations: ATM=Ataxia Telangiectasia Mutated gene; BRCA1=Breast Cancer gene 1; BRCA2=Breast Cancer gene 2; BRIP1=BRCA1 Interacting Protein C-terminal Helicase 1 gene; CHEK2=Checkpoint Kinase 2 gene; CR=complete response; CTC=circulating tumor cell; DNA=deoxyribonucleic acid; FANCA=Fanconi Anemia Complementation Group A gene; HDAC2=Histone Deacetylase 2 gene; mCRPC=metastatic castration-resistant prostate cancer; ORR=objective response rate; OS=overall survival; PALB2=Partner and Localizer of BRCA2 gene; PCWG3=Prostate Cancer Working Group 3; PR=partial response; PSA=prostate specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiographic progression-free survival; SSE=symptomatic skeletal event

Hypothesis

Niraparib will demonstrate a >15% ORR in subjects with mCRPC and DNA-repair anomalies who have measurable disease.

OVERVIEW OF STUDY DESIGN

This is a Phase 2, multicenter, open-label study to assess the efficacy and safety of once daily dosing of 300 mg niraparib in male subjects over the age of 18 years with mCRPC and DNA-repair anomalies who have received prior taxane-based chemotherapy and AR-targeted therapy.

The study will assess up to approximately 120 subjects with measurable disease who are either biallelic BRCA/non-BRCA according to a sponsor-validated blood- or tissue-based assay or who have a germline pathogenic BRCA mutation (approximately 75 subjects with DNA-repair anomalies in BRCA [BRCA1 or BRCA2] and approximately 45 subjects with DNA-repair anomalies in non-BRCA [ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2]). In addition, at least 90 subjects with non-measurable disease (ie, bone disease only) regardless of their DNA anomaly (ie, BRCA or non-BRCA) will be included to evaluate the activity of niraparib in this population. Efficacy objectives will be evaluated on subjects who have either biallelic DNA-repair anomalies as determined by a sponsor-validated blood- or tissue-based assay or germline pathogenic BRCA (BRCA1 or BRCA2) mutation. All subjects will be monitored for safety during the study period, and up to 30 days after the last dose of study drug. Treatment will continue until disease progression, unacceptable toxicity, death, or the sponsor terminates the study.

The study will consist of 5 phases; a Prescreening Phase, a Screening Phase, a Treatment Phase, a Follow-up Phase, and a Long-term Extension Phase.

SUBJECT POPULATION

Male subjects over the age of 18 years with mCRPC and DNA-repair anomalies who have received prior taxane-based chemotherapy and AR-targeted therapy are eligible for the study.

DOSAGE AND ADMINISTRATION

The study drug, niraparib 300 mg, will be provided as capsules (3 x 100 mg) for once daily oral administration. The capsules must be swallowed whole. Subjects should take their dose in the morning (with or without food).

EFFICACY EVALUATIONS

The efficacy evaluations include the following:

- Tumor measurements:
  - Chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans and whole body bone scans (^{99m}Tc). Imaging will be assessed by the investigator and these results will be used for the primary endpoint analyses. Scans will also be collected and stored by a central vendor for central review if indicated.
- serum PSA
- CTC
- survival status
- SSEs

PHARMACOKINETIC EVALUATIONS

Sparse PK sampling will be collected from all subjects in this study. Blood samples to measure plasma levels of niraparib and its metabolite, M1, will be obtained on Cycle 1 Day 1 and Cycle 2 Day 1 at predose, and between 1 to 3 hours and between 4 to 6 hours postdose.

PATIENT-REPORTED OUTCOMES EVALUATIONS

PROs will be measured as per the Time and Events Schedule utilizing paper versions of the Brief Pain Inventory - Short Form questionnaire (BPI-SF), the Functional Assessment of Cancer Therapy-Prostate questionnaire (FACT-P), and the Euro-QoL questionnaire (EQ-5D-5L).

BIOMARKER EVALUATIONS

Biomarker evaluations will be conducted as specified in the Time and Events Schedule. CTCs will be evaluated for response to study drug. Whole blood for RNA may be used to evaluate potential mechanisms of resistance that may be observed following treatment with niraparib. Circulating tumor DNA (ctDNA) may be used to screen for changes in the levels or types of DNA-repair anomalies observed over time, to monitor for potential markers of resistance to niraparib, and for concordance and bridging studies with tumor tissue.

SAFETY EVALUATIONS

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, ECOG PS, and other safety evaluations at specified timepoints as described in the Time and Events Schedule.

STATISTICAL METHODS

For the primary objective with ORR endpoint in subjects with measurable mCRPC and DNA-repair anomalies in BRCA1 or BRCA2, the null hypothesis that the ORR is ≤15% will be tested against the alternate hypothesis that the ORR is ≥32%. Efficacy of niraparib will be declared if the lower bound of the 2-sided 95% Confidence Interval (CI) for ORR is >15%. With approximately 75 subjects with measurable disease and DNA-repair anomalies in BRCA (BRCA1 or BRCA2), the study will have over 90% power such that the lower limit of the 95% CI for ORR exceeds 16%. Assuming an enrollment duration of approximately 24 months, it is anticipated that the final analysis for ORR will occur at approximately 30 months (approximately 6 months from last subject enrolled).

For the secondary objective with ORR endpoint in subjects with measurable mCRPC and DNA-repair anomalies in biallelic non-BRCA (ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2), the null hypothesis that the ORR is ≤15% will be tested against the alternate hypothesis that the ORR is ≥32%. With a 1-sided α of 0.05 and power of 80%, up to 45 subjects with measurable mCRPC and DNA-repair anomalies in biallelic non-BRCA (ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2) are to be enrolled based on Simon's two-stage design. At end of Stage 1, approximately 14 subjects will be evaluated for ORR after at least 1 post-treatment scan and a confirmatory scan for Stage 1. Future enrollment in this group may be terminated if 2 or fewer responses are observed in the first stage. Otherwise, enrollment may proceed to the second stage with a total of 45 subjects combined for the 2 stages, and the null hypothesis will be rejected if 10 or more responses are observed.

Assuming the historical CTC response rate (CTC RR) of 20% (based on unpublished data from Study COU-AA-301) and the target CTC RR of 40%, at least 60 subjects with non-measurable disease will be required to provide a lower bound of the 2-sided 95% CI greater than 20%, with a probability of 0.9.

Efficacy Analyses

The primary endpoint, ORR, will be calculated, and its 2-sided 95% exact CI will also be presented. The final analysis for ORR will be performed approximately 6 months after the last subject with measurable disease receives his first dose of study medication.

Pharmacokinetics and Exposure-Response

A population PK analysis of plasma concentration-time data of niraparib will be performed using nonlinear mixed-effects modeling to estimate oral clearance (CL/F) and oral volume of distribution (V/F). Other PK parameters may be evaluated as appropriate.

Safety Analyses

Subjects who receive at least 1 dose of study drug will be analyzed for safety. The safety parameters to be evaluated are the incidence, intensity, and type of AEs, vital signs measurements, ECGs, physical examination (abnormalities will be recorded as AEs), and clinical laboratory results.

TIME AND EVENTS SCHEDULE

See Attachment 7 for procedures to be followed during the Long-term Extension (LTE).

PHASE	Prescreening	Screening	Treatment														Follow-up
CYCLE (treatment cycle is defined as 28 days)	Any time prior to the Screening Phase	Up to 28 days prior to Cycle 1 Day 1 unless otherwise specified	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycles ≥8		EoT Visit[a]	Every 12 weeks
														Every cycle	Every 3 Cycles (eg, Cycles 10, 13, 16)		
CYCLE DAY	*Unless otherwise specified, study visits have a ±3-day time window*		1	8	15	22	1	15	1	1	1	1	1	1	1	(±5 days)	(±2 weeks)
Prescreening informed consent	X																
Biomarker panel[b]	X	X															
Prescreening AEs[c]	X																
Main study informed consent[d]		X															
Inclusion/exclusion criteria		X															
Demographics	X	X															
Medical history	X[e]	X															
Serum testosterone		X															
Whole blood for cytogenetics[f]		X															
ECG[g]		X	X				X		X	X	X	X	X		X	X	
Physical examination, vital signs (temperature, heart rate)		X	X				X		X		X		X		X	X	
Blood Pressure		X	X				X		X	X	X	X	X	X		X	
ECOG PS		X	X				X		X		X		X		X	X	
Dispensation of study drug			X				X		X	X	X	X	X	X			
Treatment compliance							X		X	X	X	X	X	X		X	
CT or MRI; Bone scan (^{99m}Tc)[h]		X	*From Cycle 1 Day 1, imaging will be performed every 8 weeks for the first 24 weeks and then every 12 weeks thereafter.*													X[h]	X
PSA		X	X				X		X	X	X	X	X		X	X	

PHASE	Prescreening	Screening	Treatment														Follow-up
CYCLE (treatment cycle is defined as 28 days)	Any time prior to the Screening Phase	Up to 28 days prior to Cycle 1 Day 1 unless otherwise specified	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycles ≥8		EoT Visit[a]	Every 12 weeks
														Every cycle	Every 3 Cycles (eg, Cycles 10, 13, 16)		
CYCLE DAY	*Unless otherwise specified, study visits have a ±3-day time window*		1	8	15	22	1	15	1	1	1	1	1	1	1	(±5 days)	(±2 weeks)
BPI-SF; FACT-P, EQ-5D-5L[i]		X	X						X		X		X		X	X	
Clinical safety laboratory tests[j]		X	X	X	X	X	X	X	X	X	X	X	X	X[j]		X	
Sparse PK sampling[k]			X		X		X		X	X	X		X				
Circulating Tumor Cells		X	X[l]				X		X	X	X	X	X			X[m]	
Whole blood for RNA			X[l]						X				X			X[m]	
Plasma for ctDNA		X	X[l]													X[m]	
SSE and Survival Status			*Collected from signing the ICF up to and beyond 30 days after last dose of study drug (including during the Follow-up Phase)*														
AEs/SAEs and con meds			*Collected from signing the ICF until 30 days after last dose of study drug*														
Related SAEs (including diagnosis of MDS/AML)			*Collected from signing the ICF up to and beyond 30 days after last dose of study drug (including during the Follow-up Phase) until resolution*														

AE=adverse event; AML=acute myeloid leukemia; BPI-SF = Brief Pain Inventory - Short Form questionnaire; con meds=concomitant medications; CT=computed tomography; ctDNA=circulating tumor DNA; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EoT=End-of-Treatment; EQ-5D-5L=Euro-QoL questionnaire; FACT-P=Functional Assessment of Cancer Therapy-Prostate questionnaire; HIV=human immunodeficiency virus; ICF=informed consent form; IHC=immunohistochemistry; MDS=myelodysplastic syndrome; MRI=magnetic resonance imaging; PK=pharmacokinetics; PRO=Patient-reported Outcome; PSA=prostate specific antigen; RNA=ribonucleic acid; SAE=serious adverse event; SSE=symptomatic skeletal event; ^{99m}Tc=technetium-99m;

[a] **EoT Visit**: An EoT visit must occur 30 (±5) days after the last dose of study drug or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. (Note: for subjects with a dose interruption who discontinue study drug, the EoT visit must occur within 30 [±14] days after the last dose of study drug).

[b] **Biomarker panel**: Blood and tissue samples will be collected for evaluation of biomarker-positivity during the Prescreening or Screening Phase (see Sections 9.1.2 and 9.7). Results obtained from the sponsor-validated assays from other Janssen-sponsored trials can be used to enter screening for this trial. Subjects who are positive for germline pathogenic BRCA1 or BRCA2 mutations will be allowed to be screened and enter the treatment phase based on local test results (blood or saliva) and will be tested by the sponsor-validated assay retrospectively. Subjects who are positive for somatic pathogenic BRCA1 or BRCA2 mutations by local test results (blood, saliva, or tissue) must be confirmed as positive by the sponsor-validated assay during screening before being able to enter the treatment phase.

[c] **Prescreening AEs:** AEs and serious AEs related to blood or recent tumor tissue collection procedures, as well as death from any cause, will be collected for 30 days after the procedures for subjects who sign the prescreening consent.

[d] **Main study informed consent**: Main study consent must be signed prior to the conduct of any study-related procedures in the Screening Phase.

[e] **Medical History**: Medical history obtained during the Prescreening Phase will be disease-specific only.

[f] **Whole blood for cytogenetics**: A blood sample collected at screening will be stored for evaluation if the sponsor's medical monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the subject develops MDS/AML). The screening mutation profile will be analyzed to determine whether any mutations were present prior to study treatment. Details on sample collection and analysis are in the laboratory manual.

[g] **ECGs**: Standard 12-lead ECGs will be performed at screening, at every cycle through Cycle 7, at every 3 cycles thereafter, at the EoT visit, and as clinically indicated (see Section 9.9 for details of ECG collection). Any known electrolyte imbalance should be treated prior to performing the ECG.

[h] **CT or MRI; Bone scan**: Chest, abdomen, and pelvis CT or MRI scans and whole body bone scans (^{99m}Tc) must be evaluated at screening. Scans performed ≤8 weeks prior to Cycle 1 Day 1 may serve as screening scans. Subjects may have imaging performed within ±3 days of visits requiring images. After first documentation of objective response for soft tissue disease, repeat imaging is required 4 weeks later (+ 2 weeks) for confirmation per RECIST 1.1. Details for the timing of subsequent scans are provided in Section 9.2.1. Progression of bone disease requires, repeat imaging. Details for confirmation and repeat imaging are provided in Section 9.2.1. Any subjects who discontinue treatment due to unequivocal clinical progression must have scans performed at the EoT visit prior to subsequent therapy. CT or MRI and bone scans performed ≤6 weeks prior to the EoT visit may serve as EoT scans.

[i] **PRO Questionnaires**: If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PROs, ECGs, vital signs, and blood draw.

[j] **Clinical safety laboratory tests**: tests include hematology, chemistry, liver function, and other panels (ie, testosterone, PSA, albumin, alkaline phosphatase, and CD4 count; see Section 9.9). Tests will be done at every cycle, except for testosterone, and CD4 count (for HIV-positive subjects only), which are to be done at screening only. Required laboratory tests must be performed within ±2 days of the scheduled visit.

[k] **Sparse PK sampling**: blood samples for sparse PK sampling will be collected on Cycle 1 Day 1 and Cycle 2 Day 1 and will be obtained predose, and between 1 to 3 hours and between 4 to 6 hours postdose in all subjects. On Cycle 1 Day 15, and on Day 1 of Cycles 3, 4, 5, and 7, blood samples for PK analysis will be obtained predose only in all subjects.

[l] **Biomarker collection on Cycle 1 Day 1:** Circulating tumor cells, whole blood for RNA, and plasma for ctDNA samples are to be collected predose on Cycle 1 Day 1.

[m] **EoT visit:** Circulating tumor cells, whole blood for RNA, and plasma for ctDNA sampling will occur at the time of radiographic progression or EoT visit (whichever is first).

ABBREVIATIONS

^{99m}Tc	technetium-99m
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
ATM	Ataxia Telangiectasia Mutated gene
AUC	area under the curve
BPI-SF	Brief Pain Inventory - Short Form questionnaire
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
BRIP1	BRCA1 Interacting Protein C-terminal Helicase 1 gene
CBC	complete blood count
CHEK2	Checkpoint Kinase 2 gene
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
CTC	circulating tumor cells
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DRD	DNA-repair defects
DRC	Data Review Committee
DSB	double-stranded breaks
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EoT	End-of-Treatment
EQ-5D-5L	Euro-QoL questionnaire
FACT-P	Functional Assessment of Cancer Therapy-Prostate questionnaire
FANCA	Fanconi Anemia Complementation Group A gene
GCP	good clinical practice
GnRHa	gonadotropin releasing hormone analog
HDAC2	Histone Deacetylase 2 gene
HIV	human immunodeficiency virus
HR	homologous recombination
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
LFT	liver function test
LTE	Long-term Extension
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PALB2	Partner and Localizer of BRCA2 gene
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PCWG3	Prostate Cancer Working Group 3

PK	pharmacokinetic(s)
P-gp	P-glycoprotein
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
PSA	prostate specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SSB	single stranded break
SSE	symptomatic skeletal event
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

Niraparib is an orally available, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, with activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases.[13] Niraparib is being investigated for the treatment of ovarian, breast, and prostate tumors in patients with DNA-repair anomalies.

1.1. Background and Design Rationale

PARPs are enzymes responsible for repair of DNA single-strand breaks (SSBs) through a process called base excision repair.[1] PARP inhibition leads to an accumulation of unrepaired SSBs, which result in stalling and collapse of replication forks and, consequently, to double-stranded breaks (DSBs). Normally, DSBs are repaired through homologous recombination (HR). If not repaired, DSBs result in cell death. When tumor cells with DNA-repair defects involving the HR pathway (eg, Breast Cancer gene [BRCA]1, BRCA2) are treated with a PARP inhibitor, they are unable to efficiently and accurately repair DSBs, which creates a synthetic lethal condition.[2,7] In men with metastatic castration-resistant prostate cancers (mCRPC), tumors with DNA-repair anomalies account for approximately 20% to 30% of the sporadic cancers.[9,18]

For many years, the established standard of care for men with mCRPC was docetaxel chemotherapy.[4] More recently, androgen receptor (AR)-targeted agents such as abiraterone acetate (ZYTIGA®) in combination with prednisone and enzalutamide (XTANDI®) have improved time to progression and survival rates, when indirectly compared to docetaxel.[10] However, there remains a subset of patients who either do not respond, or become refractory to these treatments. No approved therapeutic options are currently available for such patients. Platinum-based chemotherapy has been tested in a number of clinical studies in molecularly unselected prostate cancer patients with limited results and significant toxicities.[3,5] PARP inhibition may be a treatment option for mCRPC patients with DNA-repair anomalies following chemotherapy and AR-targeted agents.

Recently, the PARP inhibitor, olaparib, was investigated in a Phase 2 study to assess efficacy and safety in patients with mCRPC post-chemotherapy and AR-targeted agents.[16] Genetic sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes, including, but not limited to BRCA1, BRCA2, Ataxia Telangiectasia Mutated gene (ATM), Fanconi anemia genes, and Checkpoint Kinase 2 gene (CHEK2) in tumor samples.[16] Sixteen of 49 patients had a response (33%; 95% confidence interval [CI]: 20%, 48%). Response was defined as one or more of the following: objective response, circulating tumor cell (CTC) conversion, or prostate specific antigen (PSA) decline ≤50%. Of these 16 patients, 14 (88%) had a response to olaparib and were biomarker-positive for anomalies in DNA-repair genes, including all 7 patients with BRCA2 loss (4 with biallelic somatic loss, and 3 with germline mutations) and 4 of 5 patients with ATM aberrations. Conversely, only 2 of 33 biomarker-negative patient tumors (6%) had a response. Radiographic progression-free survival (rPFS) was significantly longer in the biomarker-positive group than in the biomarker-negative group (median: 9.8 versus 2.7 months, respectively). Overall survival (OS) was also prolonged in the biomarker-positive group versus the biomarker-negative group (median: 13.8 months versus 7.5 months, respectively).

Taken together, the nonclinical and clinical data, and lack of available treatment options, provide a strong rationale to investigate the role of PARP inhibition with niraparib in mCRPC patients and DNA-repair anomalies following chemotherapy and approved AR-targeted agents.

1.2. Summary of Available Nonclinical and Clinical Data

A summary of the nonclinical and clinical information available for niraparib to date is provided below. For the most comprehensive nonclinical and clinical information regarding niraparib, refer to the latest version of the Investigator's Brochure.[12]

Nonclinical Studies

In cancer cell lines that have been silenced for BRCA1 or BRCA2 genes, or that have BRCA1 or BRCA2 mutations, niraparib demonstrates anti-proliferative activity due to cell cycle arrest, followed by apoptosis. In vivo studies in mice showed that niraparib has antitumor activity against BRCA1-deficient breast cancer, BRCA2-deficient pancreatic cancer, and serous ovarian cancer.

Niraparib is not a potent inhibitor or inducer of cytochrome P450 (CYP) enzymes; therefore, it is considered to have low potential to cause drug-drug interactions. However, preclinical data show that niraparib is a weak inducer of CYP1A2 but not M1. Niraparib is a low clearance drug, and limited metabolism with involvement of multiple metabolic enzymes (both CYPs and non-CYPs) was observed in vitro. Therefore, no major changes in niraparib pharmacokinetics (PK) are expected when co-administered with modulators of CYP enzymes. Niraparib is a P-gp substrate. In animal studies, distribution of niraparib to the central nervous system (CNS) was observed; however, niraparib had no effect on neurological function in a CNS safety study using conscious mice. QTc interval was unaffected in anesthetized dogs; however, mean arterial pressure, heart rate, and QRS cardiac interval were increased. In repeat-dose toxicity studies in rats and dogs, hematologic toxicities were observed but resolved by the end of the recovery period (typically 15 to 28 days).

Clinical Studies

Niraparib is currently being investigated in ongoing Phase 2 and 3 registration clinical studies in ovarian and breast cancer. Niraparib has been evaluated in 144 subjects in Phase 1 studies (as a monotherapy and in combination). In Study PN001, 104 subjects with solid tumors, including subjects with prostate cancer (n=23) were evaluated at doses up to 400 mg once daily. Dose-proportional PK with an elimination half-life of 30 to 40 hours were observed. Antitumor activity with niraparib was observed in subjects at dose levels ranging from 60 to 400 mg. The dose limiting toxicity at 400 mg once daily was thrombocytopenia; the maximum tolerated dose and recommended Phase 2 dose for further development of niraparib was 300 mg.

In Study PN001, all subjects (104) were reported with adverse events (AEs) and 90% of subjects were reported with drug-related AEs. Serious AEs (SAEs) were reported in 34% of subjects and 10% of subjects were reported with drug-related SAEs. Only 3% of subjects discontinued treatment due to drug-related SAEs. The most common AEs (>30%) were nausea (57%), fatigue (56%), anemia (49%), constipation and vomiting (39% each), thrombocytopenia (35%), and decreased appetite (34%). The AEs responsible for discontinuation were electrocardiogram (ECG)

QT prolonged, fatigue, thrombocytopenia, intestinal obstruction, neoplasm malignant (disease progression), papilledema, pneumonitis, and vomiting. Six subjects died during the study: 4 due to disease progression, 1 due to sepsis, and 1 due to cerebral infarction. The safety profile of niraparib demonstrates AEs primarily within the blood and lymphatic and gastrointestinal System Organ Classes that are generally mild to moderate in severity and resolve with dose reduction/discontinuation.

1.3. Benefit/Risk Assessment

Niraparib, administered as monotherapy, is anticipated to have a positive benefit-risk profile when used for the treatment of patients with mCRPC and DNA-repair anomalies, as proposed for this study. This assessment is based on the following:

- During clinical development in subjects with advanced solid tumors, the most common AEs (>25% of subjects) were nausea, fatigue, anemia, vomiting, thrombocytopenia, constipation, and decreased appetite. A small number of cases of myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML), including fatal cases, have been reported in clinical studies of niraparib. The safety profile of niraparib demonstrates AEs that are generally mild to moderate in severity and are manageable with dose interruption or dose reduction. Preliminary data obtained from the current study suggest a similar profile in prostate cancer to the established safety profile of niraparib in other indications, with no new safety signals being observed to date.
- Dose-proportional PK with an elimination half-life of 30 to 40 hours were observed at doses up to 400 mg once daily in patients with solid tumors and with prostate cancer. Antitumor activity with niraparib was observed in subjects at dose levels ranging from 60 to 400 mg. The dose limiting toxicity at 400 mg once daily was thrombocytopenia; the maximum tolerated dose and recommended Phase 2 dose for further development of niraparib was 300 mg.
- While niraparib is an investigational agent in the metastatic prostate cancer population, it has been approved for the treatment of ovarian cancer. The safety profile of niraparib has been characterized in clinical studies discussed in Section 1.2. Preliminary data from sponsor studies suggest that the safety profile of niraparib in patients with metastatic prostate cancer is similar to that described in the Zejula® label.[24,25] Known toxicities for niraparib include gastrointestinal events, hematological events (ie, thrombocytopenia, neutropenia, anemia), and hypertension. These toxicities are managed by monitoring the appropriate laboratory values and making the appropriate medical interventions, such as dose interruptions. The protocol also includes a targeted monitoring plan and treatment guidelines to ensure appropriate management of toxicities.

Given that the anticipated toxicities of niraparib are recognizable through medical oversight and laboratory monitoring and are able to be managed medically, and there is a potential for increased efficacy in patients with incurable mCRPC, the sponsor considers that there is a positive benefit/risk profile and strong rationale for evaluating niraparib, a PARP inhibitor, in treatment of mCRPC patients with DNA-repair anomalies.

2. OBJECTIVES, ENDPOINTS/ASSESSMENTS, AND HYPOTHESIS

2.1. Objectives and Endpoints/Assessments

Efficacy objectives will be evaluated for subjects meeting the selection criteria that are described in Table 5.

Table 1: Study Objectives and Endpoints/Assessments

Objectives	Endpoints/Assessments
Primary	
• To assess the efficacy of niraparib in subjects with measurable mCRPC and who have either biallelic DNA-repair anomalies in BRCA (BRCA1 or BRCA2) or germline BRCA	• Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with no evidence of bone progression according to the PCWG3 criteria[20]
Secondary	
• To assess the efficacy of niraparib in subjects with measurable mCRPC and DNA-repair anomalies in biallelic non-BRCA (ATM FANCA, PALB2, CHEK2, BRIP1, or HDAC2)	• Objective response rate of soft tissue (visceral or nodal disease) as defined by RECIST 1.1 with no evidence of bone progression according to the PCWG3 criteria[20]
• To assess the efficacy of niraparib in subjects with mCRPC and DNA-repair anomalies	• CTC response defined as CTC=0 per 7.5 mL blood at 8 weeks post-baseline in subjects with baseline CTC >0
• To evaluate response outcomes of niraparib in subjects with mCRPC and DNA-repair anomalies	• OS: time from enrollment to death from any cause • As defined by PCWG3:[20] – rPFS: time from enrollment to radiographic progression or death from any cause, whichever occurs first – Time to radiographic progression – Time to PSA progression – Time to symptomatic skeletal event (SSE)
• To evaluate the safety and tolerability of niraparib	• Incidence of adverse events • Clinical laboratory test results
• To evaluate duration of tumor response	• Duration of objective response: time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first
Exploratory	
• To assess the efficacy of niraparib in subjects with mCRPC and DNA-repair anomalies	• Response rate (RR): defined as 1 of the following by PCWG3:[20] – Objective response (confirmed per RECIST 1.1), or – Conversion of CTC from ≥5 cells per 7.5 mL blood at baseline to <5 cells per 7.5 mL blood nadir, confirmed by a second consecutive value obtained 4 or more weeks later, or

Objectives	Endpoints/Assessments
	– PSA decline of ≥50%, measured twice 3 to 4 weeks apart • Time to unequivocal clinical progression
• To evaluate the population PK of niraparib and exposure-response relationships	• Analysis of niraparib oral clearance (CL/F), oral volume of distribution (V/F), and derived measures of exposure (eg, area under the curve [AUC]) • Effect of demographic and physio-pathological covariates on niraparib PK parameters • Analysis of relationships between exposure and safety or efficacy endpoints.
• To evaluate the steady-state PK of niraparib and its metabolite M1	• C_{max}, T_{max}, C_{trough}, AUC_{0-24} of niraparib and its metabolite M1 in a subset of subjects
• To evaluate the concordance between tissue-based and blood-based methodologies for detection of genomic alterations	• Comparison of gene alterations in DNA from tissue and in circulating tumor DNA (ctDNA) from plasma
• To evaluate potential DNA and RNA biomarkers predictive of response and resistance	• Changes in the levels or types of DNA and RNA biomarkers observed over time
• To evaluate the effect of niraparib on circulating tumor cells (CTCs)	• Changes in CTC counts observed over time
• To evaluate subject-relevant experiences (disease-related symptoms, treatment-related symptoms, and health-related quality of life)	• Time to deterioration in subject-relevant experiences

Abbreviations: ATM=Ataxia Telangiectasia Mutated gene; AUC=area under the curve; BRCA1=Breast Cancer gene 1; BRCA2= Breast Cancer gene 2; BRIP1=BRCA1 Interacting Protein C-terminal Helicase 1 gene; CHEK2=Checkpoint Kinase 2 gene; CR=complete response; CTC=circulating tumor cell; ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; FANCA=Fanconi Anemia Complementation Group A gene; HDAC2=Histone Deacetylase 2 gene; mCRPC=metastatic castration-resistant prostate cancer; ORR=objective response rate; OS=overall survival; PALB2=Partner and Localizer of BRCA2 gene; PCWG3=Prostate Cancer Working Group 3; PD=progressive disease; PK=pharmacokinetics; PR=partial response; PSA=prostate specific antigen; RECIST= Response Evaluation Criteria in Solid Tumors; rPFS=radiographic progression-free survival; RNA=ribonucleic acid; RR=response rate; SSE=symptomatic skeletal event.

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

Niraparib will demonstrate a >15% ORR in subjects with mCRPC and DNA-repair anomalies who have measurable disease.

3. STUDY DESIGN

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

This is a Phase 2, multicenter, open-label study to assess the efficacy and safety of once daily dosing of 300 mg niraparib in male subjects over the age of 18 years with mCRPC and DNA-repair

anomalies who have received prior taxane-based chemotherapy and AR-targeted therapy. The study will assess up to approximately 120 subjects with measurable disease who are biomarker-positive, as define in Section 9.7 (approximately 75 subjects with DNA-repair anomalies in BRCA [BRCA1 or BRCA2] and approximately 45 subjects with biallelic DNA-repair anomalies in non-BRCA [ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2]). In addition, at least 90 subjects with non-measurable disease (ie, bone disease only) regardless of their DNA anomaly (ie, BRCA or non-BRCA) will be included to evaluate the activity of niraparib in this population. Efficacy objectives will be evaluated for subjects meeting the selection criteria that are described in Table 5. All subjects will be monitored for safety during the study period, and up to 30 days after the last dose of study drug. Treatment will continue until disease progression, unacceptable toxicity, death, or the sponsor terminates the study (see Section 10).

The study will consist of 5 phases; a Prescreening Phase, a Screening Phase, a Treatment Phase, a Follow-up Phase, and a Long-term Extension Phase (see Section 9.1 for details).

4. SUBJECT POPULATION

Male subjects over the age of 18 years with mCRPC and DNA-repair anomalies (biallelic mutations and germline pathogenic mutations only for BRCA1 or BRCA2 mutations) who received prior taxane-based chemotherapy and AR-targeted therapy (second-generation or later) are eligible for the study.

4.1. Prescreening Eligibility Criteria

1. Signed prescreening informed consent form (ICF).

2. Criterion modified per Amendment 3.

   2.1. Criterion modified per Amendment 6.

   2.2. Willing to provide a tumor tissue sample (archival or recently collected), and a blood sample for analysis of DNA-repair anomalies using a sponsor-validated assay.

3. Criterion modified per Amendment 3.

   3.1. Criterion modified per Amendment 5.

   3.2. Criterion modified per Amendment 7.

   3.3 Must have received or be currently on at least 1 taxane-based chemotherapy for metastatic prostate cancer and at least 1 AR-targeted (second-generation or later) therapy.

4. Criterion modified per Amendment 3.

   4.1. Criterion deleted per Amendment 4.

4.2. Inclusion Criteria

1. Male
2. >18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Signed main study ICF indicating that the subject understands the purpose of, and procedures required for, the study and is willing to participate in the study.
4. Criterion modified per Amendment 2.

   4.1. Histologically confirmed prostate cancer (mixed histology is acceptable, with the exception of the small cell pure phenotype, which is excluded).
5. Criterion modified per Amendment 2.

   5.1. Criterion modified per Amendment 3.

   5.2. Criterion modified per Amendment 5.

   5.3. Criterion modified per Amendment 6.

   5.4. Received a taxane-based chemotherapy for the treatment of metastatic prostate cancer with evidence of disease progression on or after treatment, or discontinued from a taxane-based chemotherapy due to an adverse event.
6. Criterion modified per Amendment 2.

   6.1. Criterion modified per Amendment 3.

   6.2. Criterion modified per Amendment 5.

   6.3. Criterion modified per Amendment 6.

   6.4. Criterion modified per Amendment 7.

   6.5. Received a second-generation or later AR-targeted therapy (for example, abiraterone acetate plus prednisone, enzalutamide, apalutamide) for the treatment of metastatic prostate cancer with evidence of disease progression or non-metastatic castration-resistant prostate cancer with evidence of subsequent metastasis.
7. Criterion modified per Amendment 3.

   7.1. Criterion modified per Amendment 7.

   7.2. Biomarker-positive by at least one of the following criteria (see Section 9.7):

   a. Biallelic DNA-repair anomaly (refer to Table 5) based on a sponsor-validated blood or tissue assay.

   b. Germline pathogenic BRCA1 or BRCA2 by any test (somatic local results must be confirmed as positive by the sponsor-validated assay before dosing).
8. Criterion modified per Amendment 2.

   8.1. Criterion modified per Amendment 4.

8.2. Progression of metastatic prostate cancer in the setting of castrate levels of testosterone ≤50 ng/dL on a gonadotropin releasing hormone analog (GnRHa), or history of bilateral orchiectomy at study entry defined as having one or more of the following:

a. PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination (per Prostate Cancer Working Group 3 [PCWG3] criteria).[20] The PSA level at the screening visit should be ≥1 µg/L (1 ng/mL).

b. Radiographic progression of soft tissue by RECIST 1.1 or bone disease by PCWG3 criteria[20] as defined below:

I. Soft tissue disease (measurable) by RECIST 1.1 defined as having one or more of the following:

i. Nodal disease (pelvic or extrapelvic [retroperitoneal, mediastinal, thoracic, other]) with lesions ≥1.5 cm in the short axis.

ii. Visceral disease (lung, liver, adrenal) with lesions ≥1 cm in the long axis.

II. Bone disease (non-measurable) defined as having bone lesions in the absence of measurable soft tissue disease.

9. Must be able to continue GnRHa during the course of the study if not surgically castrate.

10. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤2 (see Attachment 3).

11. Must be able to swallow whole capsules.

12. Subject must agree to use medically accepted and highly effective methods of contraception during the course of the study and for 3 months after the last dose of study drug.

13. To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must agree while on study drug and for 3 months following the last dose of study drug to:

a. Use a condom during sexual activity.

b. Not donate sperm.

14. Criterion modified per Amendment 2.

14.1. Criterion modified per Amendment 4.

14.2. Criterion modified per Amendment 5.

14.3. Criterion modified per Amendment 6.

14.4. At screening, the following laboratory parameters must be met:

a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L

b. Hemoglobin ≥9.0 g/dL

c. Platelet count ≥100 x 10^9/L

d. Serum albumin ≥3 g/dL

e. Creatinine clearance ≥30 mL/min

f. Criterion deleted per Amendment 5.

g. Serum total bilirubin ≤1.5 x upper limit of normal (ULN) or direct bilirubin ≤1 x ULN (Note: in subjects with Gilbert's syndrome, if direct bilirubin is ≤1.5 x ULN, subject may be eligible)

h. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x ULN

i. CTC count of ≥1 cells/7.5 mL blood (required only for patients with non-measurable soft tissue disease by RECIST 1.1)

4.3. Exclusion Criteria

1. Prior treatment with a PARP inhibitor.
2. Criterion modified per Amendment 2.

   2.1. Prior platinum-based chemotherapy for the treatment of prostate cancer.
3. Known history or current diagnosis of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML).
4. Criterion modified per Amendment 5.

   4.1. Symptomatic or impending cord compression, except if subject has received definitive treatment for this and demonstrates evidence of clinically stable disease.
5. Criterion modified per Amendment 5.

   5.1. Symptomatic brain metastases.
6. Known allergies, hypersensitivity, or intolerance to niraparib or its excipients (refer to Investigator's Brochure).[12]
7. Any condition for which, in the opinion of the investigator or sponsor, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
8. Known disorder affecting gastrointestinal absorption.
9. Active cancer (other than prostate cancer; or basal cell or squamous cell skin cancer, non-muscle invasive bladder cancer [stages pTaG1 and pTaG2], or any other cancer in situ currently in complete remission) within 2 years prior to Cycle 1 Day 1.
10. Criterion modified per Amendment 5.

10.1 Prior palliative radiotherapy ≤7 days prior to Cycle 1 Day 1. Radiotherapy given >7 days prior to Cycle 1 Day 1 is permitted as long as any AEs associated with radiotherapy have resolved to Grade 1 or baseline.

11. Criterion modified per Amendment 2.

    11.1. Criterion deleted per Amendment 5

12. Criterion deleted per Amendment 3.

13. History of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsades de pointes).

14. HIV-positive subjects with 1 or more of the following:

    a. Not receiving highly active antiretroviral therapy
    b. A change in antiretroviral therapy within 6 months of the start of screening (except if, after consultation with the sponsor on exclusion criterion 14.c, a change is made to avoid a potential drug-drug interaction with the study drug)
    c. Receiving antiretroviral therapy that may interfere with the study drug (consult the sponsor for review of medication prior to enrollment)
    d. CD4 count <350 at screening
    e. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening

15. Criterion modified per Amendment 2.

    15.1. Criterion modified per Amendment 6.

    15.2. ≤14 days prior to Cycle 1 Day 1 had:

    a. a transfusion (platelets or red blood cells)
    b. chemotherapy
    c. hematopoietic growth factors

16. Criterion deleted per Amendment 5.

17. Criterion modified per Amendment 5.

    17.1. Subjects with uncontrolled (persistent) hypertension defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg despite medical management.

5. TREATMENT ALLOCATION AND BLINDING

This is an open-label, single-treatment study; therefore, blinding and randomization procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

For the purpose of this study, 'study drug' refers to niraparib. All dosing information must be recorded in the electronic case report form (eCRF). The 300 mg once daily dose was chosen based on the PK, pharmacodynamics, clinical activity, safety, and tolerability profiles of niraparib,[12] and is the same as the dose under investigation in two Phase 3 studies in subjects with ovarian and breast cancer.

6.1. Study Drug Administration

The study drug, niraparib 300 mg, will be provided as capsules (3 x 100 mg) for once daily oral administration. The capsules must be swallowed whole. Subjects should take their dose in the morning (with or without food). Although not considered study medication, subjects who have not undergone surgical castration must continue to receive regularly prescribed GnRHa. Contact the sponsor's medical monitor if interruption of GnRHa is required. All GnRHa therapies should be recorded in the concomitant medication section of the eCRF.

A treatment cycle is defined as 28 days, irrespective of missed doses. Subjects will begin taking study drug on Day 1 of Cycle 1. Sufficient study drug for each treatment cycle will be distributed on the first day of each cycle. If subjects miss a dose, then that dose should be replaced if the subject remembers within an approximate 12-hour window. Otherwise, subjects should take the next dose the following day, without compensating for the missed dose. Missed doses should be recorded in the eCRF.

6.2. Dose Modification and Management of Toxicity

All dose interruptions and dose reductions (including missed doses) and the reason for the interruption/reduction are to be recorded in the eCRF. Management of toxicities should be performed as detailed in Sections 6.2.1 and 6.2.2. Once the dose of study drug is reduced, any re-escalation to a full starting dose must be discussed in advance with the sponsor's medical monitor.

6.2.1. Non-hematologic Toxicities

For subjects who develop drug-related Grade 3 or higher toxicities, treatment must be withheld and appropriate medical management per institutional standard should be instituted. Treatment with study drug must not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline. Patients experiencing treatment-related hypertensive crisis or who have a confirmed diagnosis of posterior reversible encephalopathy syndrome will have study drug permanently discontinued. Dose reduction for AE management should be performed as described in Table 2.

It is recommended that subjects be referred to a cardiologist for further evaluation if they meet any of the following criteria:

- QTcF on ECG >480 msec at any visit.
- Persistent hypertension ≥Grade 3 despite medical intervention.

Table 2: Dose reduction for Drug-related Non-hematologic Toxicities

Event	Restarting Dose
After first Grade 3 or 4 treatment-related SAE/AE	200 mg QD
After second Grade 3 or 4 treatment-related SAE/AE	100 mg QD
After third Grade 3 or 4 treatment-related SAE/AE for ≥28 days	Discontinue or contact sponsor

QD=once daily; SAE/AE=serious adverse event/adverse event

6.2.1.1. Hepatic Toxicities

Hepatic toxicities are known potential side effect of niraparib.[12] Table 3 provides dose recommendations for subjects who develop liver function test (LFT) abnormalities during treatment with niraparib. During dose interruptions, LFTs should be monitored at least weekly. For Grade ≥2 LFT abnormalities, LFTs should be monitored at least weekly until Grade 1 or baseline. For subjects being retreated, serum transaminases should be monitored at a minimum of every 2 weeks for 3 months and monthly for the next 3 months.

Table 3: Dose Modification Criteria for AST/ALT/Bilirubin Abnormalities for Niraparib

Toxicity Grade	Dose of Niraparib
Grade 1	No change.
Grade 2	No change.
Grade 3	Interrupt until return to baseline. When AST/ALT/bilirubin are confirmed Grade 1 or baseline, niraparib can be resumed at previous dose.
Recurrence Grade 3	Interrupt until return to baseline. Then, resume at one dose level reduction.
Grade 4	Must be interrupted and discussed with medical monitor.[a]
ALT=alanine aminotransferase; AST=aspartate aminotransferase [a] Must be discussed with medical monitor prior to any restart.	

If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If a subject develops severe hepatotoxicity (ALT or AST >20 x ULN) anytime while receiving niraparib, subjects should be discontinued from treatment and retreatment should not be attempted. Re-escalation of niraparib is not permitted if the dose reduction was due to elevated LFTs.

Subjects who develop a concurrent elevation of ALT >3 x ULN and a total bilirubin >2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation should be permanently discontinued from the study drug treatment.

6.2.2. Hematologic Toxicities

Dose interruption/modification criteria for hematologic toxicities will be based on the blood counts outlined in Table 4. If dose interruption or modification is required at any point on study due to hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until AE resolution (to the specified levels in Table 4). To ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 28 days after AE resolution, after which, monitoring per the Time and Events Schedule may resume.

Study drug dose modification/reduction criteria for thrombocytopenia and neutropenia will be based on the criteria outlined in Table 4. For the management of anemia, supportive measures such

as blood transfusion may be performed as deemed necessary by the investigator per institutional standard of care. If more than 1 blood transfusion is given within 4 weeks, the sponsor should be notified. For Grade ≥3 anemia, study drug should be interrupted until resolution to <Grade 3, and restarted after discussion with the sponsor to determine if a dose level reduction is required.

The site should contact the sponsor for discussion and consider discontinuation of niraparib if hematologic toxicity has not recovered to Grade 1 or baseline after 28 days of dose interruption, or a diagnosis of MDS/AML is confirmed by a hematologist.

Table 4: Dose Modification/Reductions for Hematologic Toxicity (Platelet Count and Neutrophil Count)

Toxicity Grade	Dose of Niraparib
Grade 1	No Change, consider weekly monitoring.
Grade 2	At least weekly monitoring and consider interrupting until ≤Grade 1 or baseline and then resume at same dose with recommendation of weekly monitoring for 28 days after restart.
Grade ≥3	Interrupt until ≤Grade 1 or baseline, then: • If subject was on 300 mg, restart at 200 mg (ie, 1 dose level reduction)[a] • If subject was on 200 mg dose, resume at 200 mg or 100 mg if there was rapid decline in the hematologic parameter soon after initiation of niraparib, as judged by the investigator • If subject was on 100 mg, permanently discontinue study drug Weekly monitoring for 28 days is recommended after restarting dose.
Second occurrence Grade ≥3	Interrupt until ≤Grade 1 or baseline and restart at 1 dose-level reduction.[a] Weekly monitoring for 28 days after restarting dose is recommended. If subject was on 100 mg, permanently discontinue study drug.
Third occurrence Grade ≥3	Permanently discontinue.

[a] For each dose-level reduction, decrease dose by 100 mg or 1 capsule of niraparib.

Notes:

- For subjects with a platelet count ≤10,000 cells/µL, prophylactic platelet transfusion per guidelines may be considered. For subjects taking anti-coagulant or anti-platelet therapy, consider the risk/benefit of interrupting these drugs or prophylactic transfusion at an alternative threshold such as ≤20,000 cells/µL.
- Supportive measures like blood transfusions may be performed as deemed necessary by the investigator.
- Weekly monitoring and/or interruption are not required if values return to baseline levels.
- If subject requires platelet transfusion or has neutropenic fever or neutropenia requiring granulocyte-colony stimulating factor deemed to be related to niraparib toxicity, restart at 1 dose-level reduction.

6.3. Treatment Interruptions for Planned Procedures

Niraparib should be held for at least 24 hours prior to planned procedures that require hospitalization and should be resumed only when AEs related to the procedure are improved to Grade 1 or resolved.

7. TREATMENT COMPLIANCE

A count of all study drug provided by the sponsor will be conducted during the Treatment Phase of this study. Study drug will be dispensed and dosing compliance will be assessed at study visits as described in the Time and Events Schedule. In the absence of toxicity, if the dosing compliance is not 100%, then investigators or designated study-site personnel should re-instruct subjects regarding proper dosing procedures and the subject may continue study treatment.

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (subject-by-subject accounting), and accounts of any study drug accidentally or deliberately destroyed. The amount of study drug dispensed will be recorded and compared with the amount returned. At the end of the study, reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned to the sponsor or its representative (see also Section 14.5).

8. CONCOMITANT THERAPY

Concomitant therapies must be recorded throughout the study beginning with the signing of the main study informed consent to 30 days after the last dose of study drug. All therapies different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and indication. Concurrent enrollment in another interventional investigational drug or device study is prohibited during the Treatment Phase.

8.1. Prohibited Concomitant Medications

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered:

1. Chemotherapeutic, biologic, hormonal (exception: subjects must continue GnRHa during the course of the study if not surgically castrate), or other agents with antitumor effect against prostate cancer.
2. Live virus vaccines. An increased risk of infection by the administration of live virus vaccines has been observed with conventional chemotherapy. Effects with niraparib are unknown and therefore live virus vaccines should not be administered. Note that inactivated bacterial and virus vaccines are permitted.

8.2. Restricted Concomitant Medications

1. Niraparib is a weak inducer of CYP1A2 in vitro; therefore, caution should be used with drugs that are sensitive substrates of CYP1A2 or moderately sensitive substrates of CYP1A2 with a narrow therapeutic range (refer to the Investigator's Brochure[12]; for additional information, see Attachment 5).
2. Although no large changes in the mean QTc interval (>20 msec) were detected in a study following the treatment of niraparib 300 mg once daily, caution should be used for medications that could potentially cause QT prolongation or torsades de pointes.[17]

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, biomarker, Patient-reported Outcomes (PRO), and safety measurements applicable to this study. Medical resource utilization data will also be collected; refer to Section 9.8 for details.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PROs, ECGs, vital signs, and blood draw. Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

For each subject, the maximum amount of blood drawn will not exceed 70 mL at any visit. Refer to the laboratory manual for details regarding blood volumes to be collected for each visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Prescreening Phase for Biomarker Evaluation

The Prescreening Phase will evaluate if a potential study subject is biomarker-positive for DNA-repair anomalies (see Section 9.7). All subjects will be required to sign a specific ICF for the Prescreening Phase and provide baseline demographic characteristics and disease-specific medical history. The Prescreening Phase may occur at any time for subjects with mCRPC prior to the Screening Phase.

During the Prescreening or Screening Phase, a blood sample will be collected. In addition, a tumor tissue sample (either archival or recently collected) should also be collected. If no tumor tissue is available, then the subject will be asked to have a new tumor tissue sample collected. Tissue (archival or recently collected) may also be used to determine eligibility.

If the subject is biomarker-positive by the sponsor-validated blood- or tissue-based assay, then he is eligible to enter the Screening Phase. Subjects who are positive for pathogenic BRCA1 or BRCA2 mutations based on local test results (somatic or germline) can enter the Screening Phase.

AEs and SAEs related to the blood or recent tissue collection procedures will be collected for 30 days after the procedures. Tissue samples collected during the Prescreening Phase will be analyzed for concordance with the blood-based sample results.

9.1.3. Screening Phase

All biomarker-positive subjects must sign the main study ICF prior to the conduct of any study-related procedures in the Screening Phase. Subjects who are positive for germline pathogenic BRCA1 or BRCA2 mutations based on local test results (blood or saliva) can be screened and enter the treatment phase and subjects who are positive for somatic pathogenic BRCA1 or BRCA2 mutations (blood, saliva, or tissue) based on local results must be confirmed

as positive by the sponsor-validated assay during screening before being able to enter the treatment phase.

Eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule. Screening procedures will be performed up to 28 days before Cycle 1 Day 1, unless otherwise specified. Imaging will be accepted up to 8 weeks prior to Cycle 1 Day 1. Screening clinical safety laboratory evaluations can be used for Cycle 1 Day 1 assessments if performed within 14 days of Cycle 1.

Subjects who do not meet all inclusion criteria, or who meet an exclusion criterion, may be rescreened. Rescreening is at the discretion of the investigator. Subjects who are to be rescreened must sign a new ICF before rescreening. Subjects rescreened within 28 days of planned enrollment may use the initial screening laboratory results, computed tomography (CT)/magnetic resonance imaging (MRI) and bone scans (if still within 8 weeks of Cycle 1 Day 1) to determine eligibility if not the reason for the rescreening.

9.1.4. Treatment Phase

The Treatment Phase will begin at Cycle 1 Day 1 and will continue until the study drug is discontinued. The last measurements taken on Day 1 of Cycle 1 before administration of the study drug or at screening (whichever value was last) will be defined as the baseline values. Visits for each cycle will have a ±3-day window, unless otherwise specified. Study visits will be calculated from the Cycle 1 Day 1 date, irrespective of any treatment interruptions. Subjects may have imaging performed within ±3 days of visits requiring images. Refer to the Time and Events Schedule for treatment visits and assessments during the Treatment Phase.

For PK sampling days, the subject must not take the study drug at home on the morning of study visits. Study drug should be taken at the site. Details of PK sampling days and times are provided in the Time and Events Schedule. Additional details regarding PK sampling are provided in Section 9.3. Details of blood sample handling and storage procedures for PK are provided in the laboratory manual.

Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. Study drug treatment will continue until disease progression, unacceptable toxicity, death, or the sponsor terminates the study (see Section 10). Once the subject discontinues study drug, the subject must complete the End-of-Treatment (EoT) visit within 30 (±5) days after the last dose of study drug, and enter the Follow-up Phase. (Note: for subjects with a dose interruption who discontinue study drug, the EoT visit must occur within 30 [±14] days after the last dose of study drug).

9.1.5. End-of-Treatment Visit

An EoT visit must occur 30 (±5) days after the last dose of study drug or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. (Note: for subjects with a dose interruption who discontinue study drug, the EoT visit must occur within 30 [±14] days after the

last dose of study drug). If a subject is unable to return to the site for the EoT visit, the subject should be contacted to collect AEs that occurred though 30 days after the last dose of study drug.

9.1.6. Follow-up Phase

Once a subject has completed the Treatment Phase for a reason other than radiographic progression, CT, MRI, or bone scans (^{99m}Tc) will be collected every 3 months (12 weeks ±2 weeks) from the EoT visit until confirmed radiographic progression, provided the subject has not started a subsequent treatment for prostate cancer and does not withdraw consent. If a subject has documented radiographic progression during the Treatment Phase, additional radiographic assessments are not required during the Follow-up Phase. In addition, survival follow-up and SSEs will be performed every 3 months (12 weeks ±2 weeks) either via clinic visits, telephone interview, chart review, or other convenient methods. Deaths regardless of causality and SAEs thought to be related to study drugs (including diagnosis of MDS/AML) will be collected and reported within 24 hours of discovery or notification of the event. If the follow-up information is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents.

9.1.7. Long-term Extension Phase

See Attachment 7 for the criteria for participation and procedures to be performed during the Long-term Extension Phase.

9.2. Efficacy

9.2.1. Evaluations

Efficacy evaluations will be conducted as specified in the Time and Events Schedule. Unscheduled assessments should be considered if clinically indicated, and results collected in the eCRF. The efficacy evaluations include the following:

- Tumor measurements:
  - Chest, abdomen, and pelvis CT or MRI scans and whole body bone scans (^{99m}Tc). The same imaging modality should be used throughout the evaluation of an individual subject. Imaging will be assessed by the investigator and these results will be used for the primary endpoint analyses. Scans will also be collected and stored by a central vendor for central review if indicated.
- serum PSA
- CTC
- survival status
- SSEs

9.2.2. Endpoint Criteria

Objective response of soft tissue (visceral or nodal disease) is defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (see Attachment 2) with no evidence of bone progression on bone scan according to the PCWG3 criteria:

- Tumor response of soft tissue lesions will only be evaluated for subjects with baseline measurable disease assessed by CT or MRI as defined in RECIST 1.1.
- After first documentation of soft tissue response (CR or PR), repeat imaging is required 4 weeks later (+ 2-week window) for confirmation per RECIST 1.1. The schedule for subsequent scans will be based upon Cycle 1 Day 1, and the confirmation scan will satisfy the scan requirements for the next occurring timepoint per the Time and Events Schedule.

Radiographic progression by tumor assessment should be evaluated according to RECIST 1.1 for soft tissue disease and PCWG3 for bone disease as follows:

- Progression of soft tissue lesions measured by CT or MRI as defined in RECIST 1.1.
- Progression by bone lesions observed by bone scan and based on PCWG3.[20] Bone progression is defined as one of the following, depending on what is observed at the Week 8 scan and what is observed on the confirmatory scan (which is performed ≥6 weeks later) :

1. Subject whose Week 8 scan is observed to have ≥2 new bone lesions compared with the baseline scan would fall into one of the 2 categories below:
    a. Subject whose confirmatory scan shows ≥2 new lesions compared with the Week 8 scan (ie. a total of ≥4 new lesions compared with the baseline scan) will be considered to have bone scan progression at Week 8.
    b. Subject whose confirmatory scan did not show ≥2 new lesions compared with the Week 8 scan will not be considered to have bone scan progression. The Week 8 scan will be considered as the bone scan to which subsequent scans are compared. The FIRST scan timepoint that shows ≥2 new lesions compared with the Week 8 scan will be considered as the bone scan progression timepoint if these new lesions are confirmed by a subsequent scan ≥6 weeks later.
2. For a subject whose Week 8 scan does not have ≥2 new bone lesions compared to baseline scan, the FIRST scan timepoint that shows ≥2 new lesions compared with the Week 8 scan will be considered as the bone scan progression timepoint if these new lesions are confirmed by a subsequent scan ≥6 weeks later.

Evaluation of treatment response by PSA, imaging, and CTCs performed according to PCWG3 criteria. Duration of tumor response will be assessed only for those subjects who have an objective tumor response by RECIST 1.1 (see Attachment 2). The duration of tumor response will be assessed from the first time of observed CR/PR to the date of radiographic progression, unequivocal clinical progression, or death, whichever occurs first.

See Section 10.1 for details regarding discontinuation of study medication for disease progression.

9.3. Pharmacokinetics

9.3.1. Sample Collection and Handling

Sparse PK sampling will be collected from all subjects in this study. Blood samples to measure plasma levels of niraparib and its metabolite, M1, will be obtained on Cycle 1 Day 1 and Cycle 2 Day 1 at predose, and between 1 to 3 hours and between 4 to 6 hours postdose. On Cycle 1 Day 15,

and on Day 1 of Cycles 3, 4, 5, and 7, blood samples for PK analysis will be obtained predose only in all subjects as per the Time and Events Schedule.

Other metabolite(s) of niraparib may also be measured in collected PK samples. Other measurements may be done earlier than the specified timepoints if needed. Actual dates and times of dose administration and assessments, as well as date and time of previous dose will be recorded in the laboratory requisition form. Note that if a visit has pre- or postdose samples, the date and time of the 2 samples and of the dose administered in the clinic and prior dose taken at home must be recorded. Refer to the laboratory manual for sample collection requirements, shipping instructions, and specified controlled temperatures for storage.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of niraparib and its metabolite, M1, using a validated, specific, and sensitive assay method by, or under the supervision of, the sponsor. If other metabolite(s) are analyzed quantitatively in the plasma samples, plasma concentration of the metabolites will be reported.

After completion of quantitative analysis, the remaining plasma samples will be stored at -70°C for investigative metabolite identification/profiling as deemed necessary by the sponsor (to be reported separately from this study).

9.3.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure of niraparib will be derived using population PK modeling. Baseline covariates (eg, body weight, age, creatinine clearance, race) may be included in the model, if relevant. Data from this study may be pooled with data from other clinical studies.

9.4. Patient-reported Outcomes

The goal of collecting PRO data is to explore if subjects experience treatment benefits in pain, fatigue, and or functional status. PROs will be measured utilizing the Brief Pain Inventory - Short Form questionnaire (BPI-SF), the Functional Assessment of Cancer Therapy-Prostate questionnaire (FACT-P), and the Euro-QoL questionnaire (EQ-5D-5L). All visit-specific PRO assessments are strongly encouraged to be conducted and completed before any tests, procedures, or other consultations for that visit. The PRO assessments will be captured on paper and results entered into the eCRF. Detailed instructions for administering the PRO questionnaires will be provided in a PRO manual.

9.4.1. BPI-SF

The BPI-SF (24-hour recall) includes a front and back body diagram for the subject to identify the location of his pain. The interference items measure how much pain has interfered with recent daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. BPI pain interference is scored as the mean of the 7 interference items.

9.4.2. FACT-P

The FACT-P will provide an assessment of the subject's self-reported functional status, well-being, and prostate cancer-related symptoms. The FACT-P questionnaire includes a general functional status scale (consisting of 4 subscales: physical well-being, social and family well-being, emotional well-being, and functional well-being) and a prostate cancer-specific subscale with items including urination, bowel movement, and erectile function. Total score is calculated with general function and prostate-cancer-specific scores and ranges from 0 to 156 (higher scores indicate better functional status).

9.4.3. EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group, 1990). The EQ-5D-5L is composed of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The EQ visual analog scale records the respondents' self-rated health as 'Best imaginable health state' and 'Worst imaginable health state'.

9.5. Pharmacodynamics

Pharmacodynamics assessment was removed per Amendment 3.

9.6. Pharmacokinetic/Pharmacodynamic Evaluations

Exposure-response relationship will be explored for key efficacy (eg, RR, PSA) and safety parameters as data allow.

9.7. Biomarkers

To be included in the primary efficacy population, subjects must be confirmed to be either biallelic BRCA (BRCA1 or BRCA2) by a sponsor-validated blood- or tissue-based assay or have a germline pathogenic BRCA (BRCA1 or BRCA2) mutation (archival or recently collected), see Section 9.1.2.

The biomarkers of interest for this study are listed in Table 5.

Table 5: Biomarker Panel

Genes	Definition
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
FANCA	Fanconi Anemia Complementation Group A gene
PALB2	Partner and Localizer of BRCA2 gene
CHEK2	Checkpoint Kinase 2 gene
BRIP1	BRCA1 Interacting Protein C-terminal Helicase 1 gene
HDAC2	Histone Deacetylase 2 gene
ATM	Ataxia Telangiectasia Mutated gene

9.7.1. Evaluations

Biomarker evaluations will be conducted as specified in the Time and Events Schedule and are described in Sections 9.7.1.1 to 9.7.1.5.

9.7.1.1. Tissue Analysis

Tumor tissue (either archival or recently collected) should be obtained to evaluate DRD status, and may also be used to identify markers associated with disease evolution, immune context, or response to study drugs. Tissue samples collected at screening may be used for concordance and bridging studies for the development of the assay. Furthermore, tumor tissue may be assessed for RNA signatures predictive of response to niraparib.

9.7.1.2. Circulating Tumor Cells

Blood samples for CTC enumeration will be collected at timepoints specified in the Time and Events Schedule. CTC enumeration will be evaluated at the central laboratory, to assess response to study drug.

9.7.1.3. Whole Blood for RNA

Whole blood samples will be collected as specified in the Time and Events Schedule. Multiple ribonucleic acid (RNA) transcripts found in prostate tumors are detectable in the RNA and analysis of these samples will allow evaluation of potential mechanisms of resistance that may emerge with niraparib.

9.7.1.4. Circulating Tumor DNA

Plasma samples collected during the course of treatment may be used to screen for changes in the levels or types of DNA-repair anomalies observed over time by circulating tumor DNA (ctDNA), and to monitor for potential markers of resistance to niraparib. Samples collected at screening and Cycle 1 Day 1 may be used for concordance and bridging studies with tumor tissue as well as development of the assay.

9.7.1.5. Saliva Testing

Testing via a saliva sample may be collected to evaluate for germline mutations. Subjects will be permitted to be screened and enter the treatment phase if positive for BRCA1 or BRCA2 germline pathogenic mutations.

9.8. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).

- Duration and cause of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit).
- Number and character of diagnostic and therapeutic tests and procedures.
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

9.9. Safety

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs (12-lead), physical examinations, clinical laboratory tests, ECOG PS, and other safety evaluations at specified timepoints as described in the Time and Events Schedule. Any clinically significant abnormalities persisting at the EoT visit will be followed by the investigator until resolution or death, whichever comes first.

Adverse Events

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. AEs will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples to assess the safety of study drug will be collected. The investigator must review laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. For each laboratory abnormality reported as an AE, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade 1 or to baseline values.

Required laboratory tests must be performed within ±2 days of the scheduled visit. In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the sponsor's medical monitor. The study site must receive a copy of the hematologist’s report of aspirate/biopsy findings, which must include a classification according to World Health Organization (WHO) criteria,[22] and other sample testing reports related to MDS/AML. Data from the report will be entered on the appropriate eCRF pages and the site must keep a copy of the report with the subject’s study file.

The following tests will be performed by the central laboratory as outlined in the Time and Events Schedule:

- Hematology Panel

  -CBC (hemoglobin, white blood cell count, platelets, absolute lymphocyte count, and ANC)

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine
  -magnesium
  -inorganic phosphorus
  -total protein
  -blood urea nitrogen
  -lactate dehydrogenase
  -calcium
  -glucose
  -uric acid
  -gamma glutamyltransferase
  -chloride

- Liver Functions Tests

  -AST
  -total bilirubin (if above normal, measure direct bilirubin)
  -ALT

- Other Laboratory Tests

  -testosterone (screening only)
  -albumin
  -CD4 count for HIV-positive subjects only (screening only)
  -PSA
  -alkaline phosphatase

Electrocardiogram (ECG)

Standard 12-lead ECGs will be recorded at the timepoints outlined in the Time and Events Schedule. Any known electrolyte imbalance should be treated prior to performing the ECG. ECGs should be recorded on the same device, if at all possible, to avoid ECG device variability. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the investigator. Subjects are to reside in a quiet setting without distractions (eg, television, cell phones, and staff talking) at each scheduled timepoint for ECG measurements. Subjects should rest in a supine position for at least 10 minutes before ECG collection and should refrain from talking or moving arms or legs. Clinically significant abnormalities noted at the time of screening will be documented in the subject's medical history and recorded on the eCRF. Clinically significant abnormalities noted during the Treatment Phase and at the EoT visit will be recorded on the Adverse Event section of the eCRF.

Vital Signs

Body temperature, heart rate, and blood pressure will be recorded at the timepoints outlined in the Time and Events Schedule.

Physical Examination

The screening physical examination will include, at a minimum, the general appearance of the subject, height and weight, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. During the Treatment Phase and at the EoT visit, limited symptom-directed physical examination and weight assessment is required. Only clinically relevant abnormalities found on physical examination should be recorded and reported as AEs in the eCRF.

ECOG Performance Status

The ECOG PS scale (provided in Attachment 3) will be used to grade changes in the subject's daily living activities. The frequency of ECOG PS assessment is provided in the Time and Events Schedule.

9.10. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he discontinues study drug. Subjects who discontinue study drug should complete the EoT visit within 30 (±5) days of the last dose of study drug or the end of the dose interruption period since the last dose of study drug. Subjects should ordinarily be maintained on study treatment until confirmed radiographic progression. If the subject has radiographic progression but no unequivocal clinical progression and alternate treatment is not initiated, the subject may continue on study treatment, at the investigator's discretion. Study treatment will be continued for subjects who have increasing PSA values in the absence of radiographic or unequivocal clinical progression. Although serial PSA's will be measured on this study, progression or change in PSA values is not considered a reliable measure of disease progression, and should not be used as an indication to discontinue study therapy.[20] However, a subject's study treatment must be discontinued for:

- Study drug-related toxicity as defined in Section 6.2.
- Unequivocal clinical progression defined as:
  - Deterioration in ECOG PS to Grade 3 or higher.

  - Need to initiate any of the following because of tumor progression (even in the absence of radiographic evidence of disease):
    - Alternative anticancer therapy for prostate cancer.
    - Radiation therapy.
    - Surgical interventions for complications due to tumor progression.
- Clinically significant QTcF ≥500 ms or QTc prolongation >60 ms above baseline.
- Diagnosis of MDS/AML.
- Treatment-related hypertensive crisis or posterior reversible encephalopathy syndrome
- The investigator believes it is in the best interest of the subject to discontinue study drug.
- Withdrawal of consent for continued treatment (subject's decision to discontinue for any reason).

Palliative radiation therapy for bone pain may not require a subject to be discontinued from treatment, after discussion with the medical monitor. Note: subjects who discontinue study treatment for any reason remain on study and must follow all study evaluations described in Section 9 and outlined in the Time and Events Schedule.

10.2. Withdrawal from the Study

A subject will be considered withdrawn from the study (ie, Treatment Phase, Follow-up Phase, Long-term Extension Phase) for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent for subsequent data collection
- Study is terminated by the sponsor

If a subject is lost to follow-up, effort must be made by the study-site personnel to contact the subject and determine endpoint status and the reason for discontinuation/withdrawal. The measures taken to follow up must be documented in the subjects' source documents. The informed consent will stipulate that even if a subject decides to discontinue the study drug, he will agree to be contacted periodically by the investigator to assess endpoint status. This can be done by telephone, by chart review, or by public record search if permissible by local regulations. If the subject withdraws consent for all study-related procedures, then no further contact is permitted by the investigator or the sponsor, except as permitted by local regulations.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.3. Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be

destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the statistical analysis plan (SAP).

11.1. Analysis Populations

Enrolled Population: All subjects who are enrolled into the study. This population will be used for exploring efficacy/anti-tumor activity, subject disposition and biomarker analyses.

Primary Efficacy Population: All subjects who received at least 1 dose of study drug, had either biallelic BRCA (BRCA1 or BRCA2) per the sponsor-validated blood- or tissue-based assay, or germline pathogenic BRCA (BRCA1 or BRCA2) mutation.

Safety Population: All subjects who received at least 1 dose of study drug. This population will be used for evaluating safety and treatment compliance.

Patient-report Outcomes Population (PRO): All subjects who completed the baseline assessment and at least 1 post-baseline assessment of BPI-SF, FACT-P, or EQ-5D-5L questionnaires.

Population Pharmacokinetics Populations (PK): All subjects who received 1 dose of study drug and have at least 1 blood sample obtained post-treatment.

11.2. Sample Size Determination

For the primary objective with ORR endpoint in subjects with measurable mCRPC and DNA-repair anomalies in BRCA1 or BRCA2, defined in Section 2.1, the null hypothesis that the ORR is ≤15% will be tested against the alternate hypothesis that the ORR is ≥32%. Efficacy of niraparib will be declared if the lower bound of the 2-sided 95% exact CI for ORR is >15%.[19] With approximately 75 subjects with measurable disease and DNA-repair anomalies in BRCA1 or BRCA2, the study will have over 90% power such that the lower limit of the 95% CI for ORR exceeds 16%. It is anticipated that the final analysis for ORR will occur at approximately 30 months (approximately 6 months from last subject enrolled).

For the secondary objective with ORR endpoint in subjects with measurable mCRPC and DNA-repair anomalies in biallelic non-BRCA (ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2), the null hypothesis that the ORR is ≤15% will be tested against the alternate hypothesis that the ORR is ≥32%. With a 1-sided α of 0.05 and power of 80%, up to 45 subjects with measurable mCRPC and DNA-repair anomalies in non-BRCA (ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2) are to be enrolled based on Simon's two-stage design.[14] At end of Stage 1, approximately 14 subjects will be evaluated for ORR after at least 1 post-treatment scan and a confirmatory scan for Stage 1. Future enrollment in this group may be terminated if 2 or fewer responses are observed in the first stage. Otherwise, enrollment may proceed to the second stage

with a total of 45 subjects combined for the 2 stages, and the null hypothesis will be rejected if 10 or more responses are observed.

Assuming the historical CTC response rate (CTC RR) of CCI [redacted] and the target CTC RR of 40%, at least 60 subjects with non-measurable disease will be required to provide a lower bound of the 2-sided 95% CI greater than 20%, with a probability of 0.9.

11.3. Efficacy Analyses

ORR in subjects with measurable mCRPC and DNA-repair anomalies in either biallelic BRCA (BRCA1 or BRCA2) or germline BRCA (BRCA1 or BRCA2), and ORR in subjects with measurable mCRPC and DNA-repair anomalies in biallelic non-BRCA (ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2), as defined in Section 2.1, will be calculated, and its 2-sided 95% exact CI will also be presented. For the calculation of ORR, subjects in the Primary Efficacy Population who discontinue treatment prior to any efficacy assessments will be considered as non-responders. The final analysis for ORR in subjects with measurable mCRPC and DNA-repair anomalies in BRCA1 or BRCA2 will be performed approximately 6 months after the last subject with measurable disease and DNA-repair anomalies in BRCA1 or BRCA2 receives his first dose of study medication.

The analysis for CTC RR will be tabulated and its 2-sided 95% exact CI will also be presented. The distribution of the time-to-event endpoints will be described using the Kaplan-Meier method. Additional details will be provided in the SAP.

Anti-tumor activity, such as PSA response, CTC conversion, composite response rate, will be analyzed based on subgroups of the enrolled population of biallelic, monoallelic, and indeterminant (local test results only) biomarker status. Additional details will be provided in the SAP.

11.4. Pharmacokinetic Analyses

Individual niraparib (and its metabolite, M1) concentration-time data will be listed and summarized by time and visit. In addition, a population PK analysis of plasma concentration-time data of niraparib will be performed using nonlinear mixed-effects modeling to estimate oral clearance (CL/F) and oral volume of distribution (V/F). Other PK parameters may be evaluated as appropriate. Subject characteristics of interest (eg, body weight, age, renal function) may be evaluated as potential covariates affecting PK parameters. Details of the population PK analysis results will be presented in a separate report.

11.5. Pharmacodynamic Analyses

Pharmacodynamics analyses were removed per Amendment 3.

11.6. Biomarker Analyses

The concordance of DNA-repair anomalies in genes among tumor DNA and plasma ctDNA results may be evaluated.

The association of biomarker-positivity with clinical response or time-to-event endpoints may be assessed using appropriate statistical methods, (such as analysis of variance, categorical, or survival models), depending on the endpoints. Correlation of baseline biomarker expression levels with clinical response or relevant time to-event endpoints may be performed to identify responsive (or resistant) subgroups. Appropriate details of these exploratory analyses will be included in the biomarker SAP.

11.7. Patient-reported Outcome Analyses

BPI-SF, FACT-P, and EQ-5D-5L will be summarized over time using descriptive statistics. Time to degradation (threshold to be defined in the SAP) may be analyzed using the Kaplan-Meier method.

11.8. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between measure of exposure (eg, derived AUC or predose concentrations) and key efficacy (eg, RR, PSA) and safety parameters, will be explored graphically, as data allow. In addition, the relationship may be characterized using an appropriate PK/pharmacodynamics or logistic regression model. Details will be provided in a separate report.

11.9. Medical Resource Utilization Analyses

The analysis will be prepared separately and will not be a part of the Clinical Study Report.

11.10. Interim Analysis

Refer to the SAP for any interim analyses to be conducted.

11.11. Safety Analyses

Subjects who receive at least 1 dose of study drug will be analyzed for safety. The safety parameters to be evaluated are the incidence, intensity, and type of AEs, vital signs measurements, ECGs, physical examination (abnormalities will be recorded as AEs), and clinical laboratory results.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 or later. Treatment-emergent AEs (TEAEs) are those events that occur on or worsen after first dose of study drug through 30 days after the last dose of study drug and will be included in the analysis. AEs will be summarized by System Organ Class and Preferred Term. SAEs and deaths will be provided in a listing. All AEs resulting in discontinuation, dose modification, dosing interruption, or treatment delay of study drug will also be listed and tabulated by Preferred Term. TEAEs will be summarized by System Organ Class, Preferred Term, toxicity grade, and relationship to study drug. SAEs and deaths will also be summarized. Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or an SAE.

Clinical Laboratory Tests

Clinical laboratory test results will be collected from screening through the EoT visit. Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results will be used in the summary of laboratory data. Worst toxicity grade during treatment will be presented, according to NCI-CTCAE (version 4.03 or later). A listing of subjects with any markedly abnormal laboratory results will also be provided.

Electrocardiogram (ECG)

ECG data will be summarized by ECG parameter, as appropriate. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled timepoint. The last available predose ECG will be used as baseline. Frequency tabulations of the abnormalities will be made.

Vital Signs

Descriptive statistics of pulse/heart rate, blood pressure, and temperature values and changes from baseline will be summarized at each scheduled timepoint. The percentage of subjects with values beyond clinically important limits will be summarized.

11.12. Data Review Committee

A DRC will be established for this study to review the planned analysis (see Section 11.10) and ongoing safety data. The DRC may include individuals both internal and external to the sponsor who are knowledgeable in the disease area. The DRC responsibilities, authorities, and procedures will be documented in a separate document.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs 1) starting with the signing of the prescreening ICF for AEs related to blood and recent tumor tissue collection during the Prescreening Phase, and 2) starting with the signing of the main study ICF for all other AEs (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For niraparib, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE (version 4.03 or later). Any AE not listed in the NCI-CTCAE will be graded according to the investigator’s clinical judgment using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or

incapacitation. Prevents normal everyday activities.

Grade 4, Life-threatening: Urgent intervention indicated.

Grade 5, Death: Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the serious AE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated main study ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. SAEs, including those spontaneously reported to the investigator through 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. In addition, SAEs related to blood or recent tumor tissue collection procedures, as well as death from any cause, during the Prescreening Phase will also be reported from the time the prescreening ICF is signed until 30 days after the procedure/s occur. These Prescreening Phase SAEs should only be reported to the sponsor's pharmacovigilance team using paper SAE forms and should not be entered into the eCRF. For any of these subjects who subsequently sign the main ICF, the events need to be entered into the eCRF. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 6.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough,

runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs) associated with the use of the study drug. For anticipated events reported as individual SAEs the sponsor will make a determination of relatedness in addition to, and independent of, the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, will submit a safety report in narrative format to the investigators (and the head of the institute). The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

During the Follow-up Phase of the study, deaths regardless of causality will be reported in the eCRF. SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. SAEs that occur after 30 days following the last drug administration thought to be related to study drug will be collected and reported via the Serious Adverse Event Form within 24 hours of discovery or notification of the event and documented.

12.3.3. Pregnancy

While the effect of the study drug on sperm is unknown, PARP inhibitors disrupt DNA-repair of dividing cells and niraparib was observed to be genotoxic in in vitro studies.[12] Therefore, pregnancies in partners of male subjects included in the study should be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.4. Disease Progression and Death

Progression of disease should not be considered nor should be reported as an adverse event (or serious adverse event). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements (refer to Section 12 Adverse Event Reporting and Section 13 Product Quality Complaint Handling).

As OS is an endpoint of the study, all subjects must be followed for survival until death and information relating to a subject’s death (eg, date of death and primary cause of death) should be recorded. Fatal events (regardless of relationship to study drug) should be reported as SAEs for subjects until 30 days after the last dose of study drug. Fatal events occurring after that 30-day period after the last dose of study drug will not be reported as SAEs and will be captured on the

designated case report form for survival. Death is an outcome of an AE and not an AE itself. All reports of death within 30 days after the last dose of study drug should include an AE term for the cause of death (if known).

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event. If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

The niraparib capsule supplied for this study contains 100 mg of niraparib. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.[12]

14.2. Packaging

Niraparib 100 mg capsules will be packaged in high-density polyethylene bottles with child-resistant closures.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

The study drug must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol. Subjects should be advised to keep the study drug out of reach and sight of children.

Niraparib may have adverse effects on a fetus in utero. Caregivers should handle niraparib with protection (eg, gloves). It is not known whether niraparib is present in, or has transient effects on the composition of semen. To avoid risk of drug exposure through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed while on study drug and for 3 months following the last dose of study drug. Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure
- Pharmacy manual/study-site investigational product and procedures manual
- Electronic data capture (eDC) Manual
- Laboratory manual
- Recruitment materials
- PRO questionnaires
- RECIST 1.1
- Sample prescreening ICF
- Sample main study ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is an open-label study to evaluate the efficacy and safety of niraparib in men with mCRPC and DNA-repair anomalies. While niraparib is an investigational PARP inhibitor, responses to a drug with a similar mechanism of action (olaparib; see Section 1.1) have been observed in men with mCRPC. Subjects with DNA-repair anomalies exhibited better response rates compared to subjects without DNA-repair anomalies. Given these promising clinical data, the benefit of treatment with niraparib in men with mCRPC and prospectively selected DNA-repair anomalies outweighs the potential risks involved.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

All participating subjects will receive full supportive care and will be followed closely for efficacy and safety throughout the study. As objective response is the primary endpoint, scheduled imaging is incorporated into the protocol. The timing of imaging is designed to evaluate response and capture progression events and allow the clinical investigator to make timely treatment decisions, yet balancing this with preventing subject overexposure to radiation. The frequency of scanning is consistent with requirements to assess rPFS by PCWG3 criteria.[20] A DRC will be commissioned to review the efficacy and safety of the treatment on an ongoing basis and make recommendations as to the future conduct of the study.

As with all clinical and PK studies, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, the use of intravenous indwelling catheters is permitted in this study. The blood sample collection scheme was designed to collect the minimum number of blood samples that can determine the efficacy, safety, PK, and biomarker requirements of the study. Note that the total volume of blood to be collected is an estimate (see Section 9.1.1); the actual amount may vary depending on laboratory standard procedures. The volume of blood to

be drawn is considered customary and acceptable for subjects participating in an oncology study and is deemed reasonable over the time frame of the study, based upon the standards of the WHO.[23]

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s). At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must provide consent according to local requirements after the nature of the study has been fully explained; consenting will include remote/virtual consent or written consent. Consent must be given before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. Subjects will be told that alternative

treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his survival status and agrees to allow his study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations and subsequent disease-related treatments, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, biomarker, and pharmacokinetics research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand niraparib, to understand prostate cancer in patients with DNA-repair anomalies, to understand differential drug responders, and to develop tests/assays related to niraparib and prostate cancer in patients with DNA-repair anomalies. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not enrolled into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; paper PROs; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.2, Inclusion Criteria and Section 4.3, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician, or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the

eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for case report form completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician’s office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the clinical trial agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding niraparib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a

result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of niraparib, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the

version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

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Attachment 1: Prostate Cancer Working Group 3 Criteria

Attachment removed per Amendment 3.

Attachment 2: Summary of RECIST Criteria Version 1.1 with Integration of PCWG3 for Evaluation of Response

The following information was extracted from Section 3, Section 4, and Appendix I of the New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1) authored by Eisenhauer et al (2009).[6]

3. Measurability of tumor at baseline

3.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

3.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

The following two methods of measure are not allowed in this protocol:

- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- *Malignant lymph nodes:* To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also 'Baseline documentation of target and non-target lesions' in section 4.2 of the RECIST guideline for information on lymph node measurement.

3.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.2 Specifications by methods of measurements

3.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

3.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination.

4. Tumor response evaluation

4.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements.

4.2 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al. (Reference #10 in Eisenhauer publication).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Lymph nodes merit special mention since they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The *short* axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm•30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II of the Eisenhauer reference). All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

4.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

4.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note*: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression (see comments below) of existing non-target lesions. (*Note*: the appearance of one or more new lesions is also considered progression).

4.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some Phase studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy.' If 'unequivocal progression' is seen, the patient should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

4.4.1 Timepoint response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 in this attachment provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

For all timepoints when patients have non-measurable (therefore non-target) disease only, the RECIST 1.1 and PCWG3 timepoint response will be integrated to determine the overall timepoint response.

4.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of progressive disease. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion.

4.4.3 Best overall response: all timepoints

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 1: Overall Timepoint Response - Subjects with Target (+/- Non-target) Disease +/- Bone Disease

Target lesions	Non-target lesions	New lesions	Overall RECIST v1.1 response (nodal/visceral)	Best overall response RECIST v1.1 when confirmation is required[a]	Overall PCWG3 response (bone, when applicable)	Overall radiographic response
CR	CR	No	CR	≥4 wks. Confirmation[b]	CR = Non-PD + no focal uptake (lesion count = 0)	CR
CR	CR	No	CR	≥4 wks. Confirmation[b]	SD = Non-PD	PR
CR	CR	No	CR	≥4 wks. Confirmation[b]	PD	PD
CR	Non-CR/non-PD	No	PR	≥4 wks. Confirmation[b]	CR = Non-PD + no focal uptake (lesion count = 0)	PR
CR	Non-CR/non-PD	No	PR	≥4 wks. Confirmation[b]	SD = Non-PD	PR
CR	Non-CR/non-PD	No	PR	≥4 wks. Confirmation[b]	PD	PD
CR	Not evaluated	No	PR	≥4 wks. Confirmation[b]	CR = Non-PD + no focal uptake (lesion count = 0)	PR
CR	Not evaluated	No	PR	≥4 wks. Confirmation[b]	SD = Non-PD	PR
CR	Not evaluated	No	PR	≥4 wks. Confirmation[b]	PD	PD
CR	CR	No	CR	≥4 wks. Confirmation[b]	NE (i.e. poor scan quality, superscan)	NE
PR	Non-CR/Non-PD/ not evaluated	No	PR	≥4 wks. Confirmation[b]	CR = Non-PD + no focal uptake (lesion count = 0)	PR
PR	Non-CR/Non-PD/ not evaluated	No	PR	≥4 wks. Confirmation[b]	SD = Non-PD	PR
PR	Non-CR/Non-PD/ not evaluated	No	PR	≥4 wks. Confirmation[b]	PD	PD
PR	Non-CR/Non-PD/ not evaluated	No	PR	≥4 wks. Confirmation[b]	NE (i.e. poor scan quality, superscan)	NE
SD	Non-PD or not all evaluated	No	SD	SD	Any except PD	SD
SD	Non-PD or not all evaluated	No	SD	SD	NE (i.e. poor scan quality, superscan)	NE
Not all evaluated	Non-PD	No	NE	NE	Any except PD	NE
Not all evaluated	Non-PD	No	NE	NE	PD	PD
Not done			NA	NA	Non-PD	NE
					PD	PD
					NE	NE
CR	CR	No	CR	≥4 wks. Confirmation[b]	Not done	NE
CR	CR	No	CR	≥4 wks. Confirmation[b]		NE
CR	CR	No	CR	≥4 wks. Confirmation[b]		NE
CR	Non-CR/non-PD	No	PR	≥4 wks. Confirmation[b]		NE
CR	Non-CR/non-PD	No	PR	≥4 wks. Confirmation[b]		NE
CR	Non-CR/non-PD	No	PR	≥4 wks. Confirmation[b]		NE
CR	Not evaluated	No	PR	≥4 wks. Confirmation[b]		NE

Target lesions	Non-target lesions	New lesions	Overall RECIST v1.1 response (nodal/visceral)	Best overall response RECIST v1.1 when confirmation is required[a]	Overall PCWG3 response (bone, when applicable)	Overall radiographic response
CR	Not evaluated	No	PR	≥4 wks. Confirmation[b]		NE
CR	Not evaluated	No	PR	≥4 wks. Confirmation[b]		NE
SD	Non-PD or not all evaluated	No	SD	SD		NE
SD	Non-PD or not all evaluated	No	SD	SD		NE
Not all evaluated	Non-PD	No	NE	NE		NE
Not all evaluated	Non-PD	No	NE	NE		NE
PD	Any	Yes or No	PD	PD		PD
Any	PD[c]	Yes or No	PD	PD		PD
Any	Any	Yes	PD	PD		PD
PD	Any	Yes or No	PD	PD	Any	PD
Any	PD[c]	Yes or No	PD	PD	Any	PD
Any	Any	Yes	PD	PD	Any	PD

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable; wks=weeks

a. See Eisenhauer et al for further details on what is evidence of a new lesion.[6]
b. Only for non-randomized studies with response as primary endpoint.
c. Unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Attachment 3: ECOG Performance Status

ECOG Grade Scale (with Karnofsky conversion)

0	Fully active, able to carry on all predisease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work on a light or sedentary nature, eg, light housework, office work. (Karnofsky 70-80)
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. (Karnofsky 50-60)
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead. (Karnofsky 0)

Attachment 4: Medications That Could Potentially Cause QT Prolongation or Torsades De Pointes

Attachment deleted per Protocol Amendment 3.

Attachment 5: Substrates of CYP1A2

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm[8]

http://medicine.iupui.edu/CLINPHARM/ddis/main-table[11]

Attachment 6: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-specific events) or background regimen (ADT events).

For the purposes of this study, the following events will be considered anticipated events:

Disease-specific Events	**ADT Events**
erectile dysfunction	depression
hematuria	gynecomastia
incontinence	libido decreased
lymphoedema	osteoporosis
nocturia	sexual dysfunction
painful ejaculation	testicular atrophy
prostatic specific antigen increased	
ureteric obstruction	
urethral obstruction	
urinary flow decreased	
urinary hesitation	
urinary tract obstruction	

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets SAE criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related, will undergo expedited reporting (if appropriate) per applicable clinical trial legislation to Health Authorities and IRB/ECs. If an anticipated event is considered disease-related or not related to study drug, the event will be exempt from expedited reporting. To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/ECs.

Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's

study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention based on a review of the aggregate data.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

Attachment 7: Long-term Extension Phase

The LTE Phase will begin after completion of the primary analysis and subsequent notification to the sites. The sponsor will continue to provide study drug until subjects no longer derive benefit from treatment or until further notification by the sponsor on a different means for continued supply of study treatment.

At the time of initiation of the LTE Phase, subjects who elect not to continue in the LTE Phase will be discontinued from the study within approximately 3 months from the initiation of the LTE Phase at the site. Subjects who progress and are no longer deriving clinical benefit and require subsequent treatment will be discontinued from the study and will receive such treatment at the discretion of the investigator.

The LTE Phase will begin when both Amendment 8 is approved at the site and the sponsor has notified the site of the start of the LTE.

- Subjects who are still receiving niraparib will be offered the option to continue to receive niraparib.
- Subjects who are in the Follow-up Phase of the main study will be discontinued from the study and all data collection will cease.
- Subjects must provide updated informed consent (signed form or remote) to continue in the LTE Phase of the study.

Study Treatment Administration

Study Treatment During the Long-term Extension

Study treatment will be administered orally on an outpatient basis. A treatment cycle is defined as 28 days. Sufficient study drug for each treatment cycle will be distributed as specified in Table 7.

Subjects will receive niraparib according to the schedule in Table 6. If a subject was receiving a lower dose of niraparib, he should continue on that lower dose in the LTE Phase.

Table 6: Study Treatment Administration for the Long-term Extension Phase

Study Treatment	Daily Dose	Schedule
Niraparib	300 mg (3×100 mg tablets)	Once daily with or without food

If a dose of niraparib is missed, the dose should only be replaced if the subject remembers and takes the dose within a 12-hour window; otherwise, it should be omitted and should not be made up or taken with the next dose the following day.

Dose modifications for toxicity are provided in Section 6.2 of the protocol.

Prohibitions and Restrictions

Refer to protocol Sections 8.1 and 8.2 for prohibited and restricted concomitant medications.

Study Procedures for the Long-term Extension

All subjects continuing in the LTE Phase will follow the schedule of procedures outlined in Table 7.

Sites can follow the subjects for disease assessment and safety per the local practice. No efficacy data will be collected; only SAEs will be collected for safety as specified in Table 7. Based on local regulations, additional safety data may be collected.

Discontinuation Criteria for the Long-term Extension

If a subject meets the discontinuation criteria as defined in Section 10.1 of the protocol, study treatment must be discontinued.

Sections 1, 3, 6 through 8, 10, 12 through 17 of the main protocol will remain in effect, but follow the Time and Events Schedule and list of assessments in Table 7.

Table 7: Time and Events Schedule (Long-term Extension Phase With Limited Data Collection)

Procedures	Comments	Long-term Extension Phase (until subjects no longer derive benefit or termination of the study)
Screening		
Informed consent	All subjects must sign the ICF for the LTE Phase	X (before starting the LTE)
Study Drug Dispensing		
Niraparib	Subjects will receive open-label niraparib	Continuous; sufficient study drug until next visit will be dispensed
Study drug compliance		X (via IWRS)
Clinical Laboratory		
Hematology and blood chemistry		Per local practice and local label for niraparib or the USPI/EU SmPC
Safety		
SAEs		Collection via GMS database (see Section 12.3.2)

EU SmPC=European Union Summary of Product Characteristics; GMS=Global Medical Safety; ICF=informed consent form; IWRS=interactive web response system; LTE=Long-term Extension; SAE=serious adverse event; USPI=United States Prescribing Information

INVESTIGATOR AGREEMENT

JNJ-64091742 (niraparib)
Clinical Protocol 64091742PCR2001 Amendment 8

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature PPD Date: PPD
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 17 July 2020