Janssen Research & Development *

Clinical Protocol

A Phase 1b-2 Study of Niraparib Combination Therapies for the Treatment of Metastatic Castration-Resistant Prostate Cancer

QUEST

Protocol 64091742PCR2002 Phase 1b-2
Amendment 7

JNJ-64091742 (niraparib)

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312)

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Prepared by: Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	11 October 2017
Amendment 1	07 December 2017
Amendment 2	22 May 2018
Amendment 3	28 November 2018
Amendment 4	18 December 2019
Amendment 5	04 March 2020
COVID-19 Appendix	17 April 2020
Amendment 6	29 October 2020
Amendment 7	03 August 2021

Amendment 7 (03 August 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is to add a Long-term Extension (LTE) Phase to allow subjects who benefit from the study treatment (Combination 1 or 2 or 3) to continue to receive the same study treatment after the primary analysis is completed.

In conjunction with the start of the Long-term Extension Phase and given the well-characterized safety profile of niraparib in the different combinations explored, data collection will be minimal, to lower the burden to subjects.

Section Number and Name	Description of Change	Brief Rationale
Synopsis (Overview of Study Design); 3.1. Overview of Study Design; 3.1.4. Long-term Extension Phase for any Combination Subgroup; 9.1.1. Overview; 9.1.4.1. Long-term Extension Phase With Minimal Data Collection	Added text to include the Long-term Extension Phase in the study design.	To provide detailed information for the Long-term Extension Phase.
3.1. Overview of Study Design	It was specified that each combination study will now have 5 phases.	
3.1. Overview of Study Design; 3.1.4. Long-term Extension Phase for any Combination Subgroup; 9.1.1. Overview; 9.1.4.1. Long-term Extension Phase With Minimal Data Collection	Referred to the new Attachment 7 for details of the Long-term Extension Phase.	
3.1.1. Combination 1: Niraparib and Cetrelimab	Added a note in the footnote of Figure 1 and Figure 2 to specify that the Long-term Extension Phase is not included in the schematic for Combination 1 and Combination 2.	

Section Number and Name	Description of Change	Brief Rationale
(Figure 1); 3.1.2. Combination 2: Niraparib and AAP (Figure 2)		
9.1.4.1. Long-term Extension With Minimal Data Collection (new subheading)	Provided information on the Long-term Extension Phase with minimal data collection.	
Attachment 7: Long-term Extension Phase (new attachment)	This attachment includes detailed information, including a Time and Events Schedule, for the Long-term Extension Phase with minimal data collection.	
Attachment 8: Protocol Amendment History	The protocol amendment 6 summary table was moved to Attachment 8.	To align with the template requirement.
Throughout the protocol	Minor formatting and spacing corrections were made.	Minor errors were noted.

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SYNOPSIS

A Phase 1b-2 Study of Niraparib Combination Therapies for the Treatment of Metastatic Castration-Resistant Prostate Cancer

Niraparib is an orally available, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, with potent activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases. In this study, the sponsor intends to investigate niraparib in combination with other agents. This protocol will describe the overall conduct of the study, which will begin with niraparib in combination with anti-PD-1 monoclonal antibody, cetrelimab (JNJ-63723283) (Combination 1). The second combination to be studied is niraparib in combination with ZYTIGA® (abiraterone acetate [AA]) plus prednisone (referred to as AAP) (Combination 2). Under Amendment 4, enrollment into Combination 2 was closed. Under Amendment 6, enrollment into Combination 1 (Cohort 1A and Cohort 1B) is closed. The third combination to be studied is niraparib plus abiraterone acetate in 2 fixed-dose combination (FDC) tablets (CJNJ-67652000) (Combination 3). The sponsor may amend this protocol in future to investigate additional niraparib combination therapies, if and when scientific data are available to support such studies.

OBJECTIVES, ENDPOINTS, AND HYPOTHESES- Combinations 1 and 2

Primary Objectives and Endpoints for Part 1*

Objectives	Endpoints
Primary	
• To evaluate the tolerability of niraparib combination therapies for the treatment of mCRPC • Determine the RP2D of niraparib combination therapies	• Incidence of specified toxicities

mCRPC=metastatic castration-resistant prostate cancer; RP2D=recommended Phase 2 dose
*The RP2D for niraparib and AAP was established in the sponsor Study 64091742PCR1001 (see Section 1.3.2). Therefore, Part 1 (dose-finding) was not conducted in this study for Combination 2.

Primary Objectives and Endpoints for Part 2

Objectives	Endpoints
Primary	
• To evaluate the antitumor effect of the RP2D of niraparib combination therapies for the treatment of mCRPC	• Combination 1: Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by RECIST 1.1 with no evidence of bone progression according to PCWG3 criteria • Combination 2: Composite response rate (RR): defined as 1 of the following by PCWG3:[50] Objective response (confirmed per RECIST 1.1), or CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline,

Objectives	Endpoints
	confirmed by a second consecutive value obtained 4 or more weeks later, or – PSA decline of ≥50%, measured twice 3 to 4 weeks apart
• To evaluate the safety of the RP2D of niraparib combination therapies for the treatment of mCRPC	• Incidence and severity of AEs

AE=adverse event; CTC=circulating tumor cells; mCRPC=metastatic castration-resistant prostate cancer; ORR=objective response rate; PCWG3=Prostate Cancer Working Group 3; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose

Hypotheses

Part 1 (Safety Run-in): An RP2D of niraparib when combined with other anticancer agents can be identified.

Part 2 (Dose Expansion): Niraparib administered in combination with other anticancer agents at the selected RP2D is safe and has antitumor activity.

The hypotheses specific to Combination 1 are as follows:

- That cetrelimab inhibition of PD-1 complements the antitumor activity of the PARP inhibitor, niraparib, for effective and safe treatment of subjects with metastatic castration-resistant prostate cancer (mCRPC) and DNA-repair gene defects (DRD) or CDK12 pathogenic alterations.
- The combination of niraparib and cetrelimab is safe and has antitumor activity in subjects with mCRPC who do not have DRD or CDK12 pathogenic alterations.

The hypothesis specific to Combination 2 is as follows:

- Androgen receptor (AR) inhibition enhances the antitumor activity of PARP inhibition for the effective and safe treatment of subjects with mCRPC and DRD.

OBJECTIVES, ENDPOINTS, AND HYPOTHESES- Combination 3

Objectives	Endpoints
Primary	
• To determine the relative bioavailability of 2 regular-strength FDC tablet formulations of niraparib and AA with respect to niraparib and AA co-administered as SA under fasted conditions in subjects with mCRPC	• PK parameters (C_{max}, $[C_{max}/dose]_{niraparib}$, $AUC_{0\text{-}168h}$, $[AUC_{0\text{-}168h}/dose]_{niraparib}$) of niraparib and AA after a single dose
Secondary	
• To evaluate the PK of a low-strength FDC tablet formulations of niraparib and AA under fasted conditions in subjects with mCRPC • To assess the safety of niraparib in combination with AA in subjects with mCRPC	• PK parameters (C_{max}, $[C_{max}/dose]_{niraparib}$, $AUC_{0\text{-}168h}$, $[AUC_{0\text{-}168h}/dose]_{niraparib}$) of niraparib and AA after a single dose • Adverse events and clinical laboratory safety

AA=abiraterone acetate; $AUC_{0\text{-}168h}$=area under the plasma concentration versus time curve over 7 days; C_{max}= maximum observed plasma concentration after a single dose; FDC=fixed-dose combination; mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetic; SA=single agent

Hypothesis

Combination 3 is an estimation study to assess the relative bioavailability (BA) of niraparib and AA as FDC tablet formulations compared to single agents (SA) under fasted conditions by providing the point estimate and associated precisions of the geometric mean ratios (GMRs) between the FDC test formulations and the SA reference formulation for the primary pharmacokinetic (PK) parameters. No formal hypothesis will be tested.

OVERVIEW OF STUDY DESIGN

This is a Phase 1b-2, multicenter, open-label study to select the RP2D of niraparib in combination with other anticancer agents, followed by dose expansion that will enroll adult subjects with mCRPC. Combination 3 includes a BA assessment as described below.

Combination 1

For Part 1, at least 6 evaluable subjects will be treated with niraparib 200 mg orally once daily in combination with cetrelimab 480 mg IV once every 4 weeks. The sponsor may choose to enroll subjects to additional dose regimens (ie, at least 6 additional evaluable subjects with cetrelimab and a modified dose of niraparib [ie, 100 mg or 300 mg]), depending on the available data with the niraparib 200 mg cohort.

Once an RP2D has been established for the combination in Part 1, approximately 30 subjects will be enrolled per cohort for Part 2. All subjects will be assigned to a cohort based on their biomarker status for DRD (ie, Cohort 1A=BM+ or Cohort 1B=BM-) or BM+ for CDK12 pathogenic alterations, which will be determined during the prescreening phase using a blood or tissue assay (as it becomes available). Note that a futility analysis was performed for Cohort 1B after approximately 10 subjects were enrolled and evaluated in Part 2. Based on the futility analysis conducted, a response rate (RR) of 13% was not achieved. Accordingly, the biomarker negative cohort (Cohort 1B) was closed to new enrollment. Subjects that are enrolled in this cohort and still on study may continue. Study-related assessments, study procedures, and data collection will be modified under Amendment 6.

Subjects with CDK12 pathogenic alterations are eligible to enroll into cohort 1A (BM+) of Combination 1 (niraparib + cetrelimab). The basis for this inclusion was data from the olaparib PROfound study. Metastatic castration-resistant prostate cancer patients who had CDK12 pathogenic alterations treated with olaparib had a median rPFS of 5.09 months compared to an rPFS of 2.20 months on either abiraterone or enzalutamide, demonstrating that patients with CDK12 pathogenic alterations achieved greater benefit from a PARP inhibitor compared to antiandrogen agents. Furthermore, Antonarakis et al. concluded that a proportion of these patients respond modestly to PD-1 inhibitors, potentially implicating CDK12 deficiency in immunotherapy responsiveness. Because CDK12 appears to define a distinctly immunogenic class of prostate cancer and also now that there is randomized clinical trial evidence that PARP inhibition confers an rPFS advantage versus standard of care hormonal therapy, the combination of these two independent mechanisms of action is expected to confer at least additive clinical benefit to the proposed eligible population.

Under Amendment 6, enrollment into Combination 1 (Cohorts A and B) is closed. Only subjects who have signed the prescreening or screening informed consent form prior to the approval date of Amendment 6 will be allowed to be enrolled if all inclusion/exclusion criteria for Combination 1A are met.

Combination 2

The RP2D for niraparib plus AAP was established as niraparib 200 mg and abiraterone acetate 1,000 mg plus prednisone 10 mg (AAP) in the sponsor study 64091742PCR1001. Therefore, Part 1 (dose-finding) was not conducted for Combination 2.

Combination 2 will explore the safety and efficacy of niraparib plus AAP in subjects with mCRPC and DRD (biallelic and monoallelic) as determined during the Prescreening Phase using a blood or tissue assay.

A total of approximately 80 subjects will be enrolled into 4 cohorts (BRCA biallelic loss [2A], other DRD biallelic loss [2B], BRCA monoallelic loss [2C], and other DRD monoallelic loss [2D]), with approximately 20 subjects in each cohort.

Under Amendment 4, enrollment into Combination 2 is closed. Only subjects who have signed the informed consent form prior to the approval date of Amendment 4 will be allowed to complete screening and be enrolled if all prescreening inclusion/exclusion criteria for Combination 2 are met. Subjects already enrolled in Combination 2 can continue to receive study medication until documented disease progression or the subject discontinues the study treatment for any reason. Under Amendment 4, study-related assessments will be per local practice, at the investigator's discretion, and limited data will be collected.

Combination 3

Combination 3 is an open-label, multi-center, partly randomized (Cohort 1 only), parallel group study to determine the PK and safety of 2 FDC tablet formulations of niraparib+AA in men with mCRPC. The study will consist of a 21-day Screening Phase to determine eligibility, an open-label PK Assessment Phase of 8 days (Study Days 1-8, inclusive), followed by an Extension Phase during which treatment with SA niraparib and AAP will be continued from Cycle 1 Day 1 (Study Day 8) until discontinuation.

During the PK Assessment Phase, 3 cohorts will be studied:

- Cohort 1: subjects (N=34) will be randomized to receive a single dose of niraparib plus AA (200 mg niraparib + 1,000 mg AA) given as FDC1 regular-strength tablet formulation (G010) (Treatment Arm B [Cohort 1B], N=17) or as SAs (Treatment Arm A [Cohort 1A], N=17). Relative BA of the FDC1 regular-strength tablet will be assessed by comparing PK results from Cohort 1A to Cohort 1B.
- Cohort 2: subjects (N=17) will be assigned to receive a single dose of niraparib plus AA (200 mg niraparib + 1,000 mg AA) as FDC2 regular-strength tablet formulation (G012) (Treatment Arm C, Cohort 2C). Relative BA of the FDC2 regular-strength tablet will be assessed by comparing the PK results from Cohort 2C to Cohort 1A.
- Cohort 3: subjects (N=17) will be assigned to receive a single dose of niraparib plus AA (100 mg niraparib + 1,000 mg AA) as a low-strength FDC1 (G009) (Treatment Arm D [Cohort 3D]) or FDC2 (G014) (Treatment Arm E [Cohort 3E]) tablet formulation. The selection of Cohort 3D or 3E will be based on the relative BA results from Cohorts 1 and 2. Relative BA of the FDC1 or FDC2 low-strength tablet formulation will be assessed by comparing the PK results from Cohort 3D or 3E, respectively, to Cohort 1A.

Long-term Extension Phase for any Combination Subgroup

The Long-term Extension Phase for the specified combination will start once the Amendment 7 has been approved at the site and after the notification by the sponsor.

EVALUATIONS

Combination 1 and Combination 2

- Antitumor 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 derived by the sponsor, and these results will be used for the primary endpoint analyses.

  serum PSA (per PCWG3)

  CTCs

survival status

- Biomarker evaluations: DRD and CDK12 will be evaluated as part of prescreening eligibility. Other exploratory biomarker analyses will be performed as appropriate.
- Safety evaluations: Safety assessments will be based on medical review of adverse event (AE) reports and the results of vital sign measurements, physical examinations, clinical safety laboratory tests, Eastern Cooperative Oncology Group Performance Score, and other safety evaluations at specified timepoints described in Time and Events Schedules.

Combination 1

- PK and immunogenicity evaluations: Blood samples will be collected to measure the plasma concentration of niraparib, and if performed, its metabolite, M1, when dosed with the combination agent. Systemic (serum or plasma) concentrations of each combination agent, and population PK parameters and derived exposure will also be determined. Anti-drug antibodies will be determined, if applicable.

Combination 3

PK evaluations: Blood samples will be collected to measure the plasma concentrations of niraparib and abiraterone.

Safety evaluations: collection of AEs and SAEs during the PK Assessment Phase (Days 1-8, up to the 168-hour PK sampling). Serious AEs only will be collected throughout the Extension Phase (from C1D1 up to discontinuation of study drug).

STATISTICAL METHODS

Statistical methods are specific to each combination.

Combination 1

For Part 1 of the study, at least 6 evaluable subjects each will be initially enrolled. Non-evaluable subjects will be replaced. For Part 2 of the study, approximately 30 subjects per cohort will be enrolled. It is anticipated that the final analysis for ORR will occur approximately 6 months after the last subject in each cohort is enrolled.

For Part 2 of the study, the primary endpoint for antitumor activity is ORR. Cohorts 1A and 1B will be evaluated and analyzed independently.

For Cohort 1A, the null hypothesis that the ORR is ≤25% will be tested against the alternative hypothesis that the ORR is ≥50%. Antitumor activity of niraparib and cetrelimab will be declared if the lower bound of the 2-sided 90% exact confidence interval (CI) for ORR is >25%. With approximately 30 BM+ subjects, Cohort 1A will have over 80% power such that the lower limit of the 90% CI for ORR exceeds 25%.

For Cohort 1B, the null hypothesis that the ORR is ≤10% will be tested against the alternative hypothesis that the ORR is ≥30%. Antitumor activity of niraparib and cetrelimab will be declared if the lower bound of the 2-sided 90% exact CI for ORR is >10%.

With Cohort 1A and Cohort 1B closed under Amendment 6 prior to reaching the originally proposed sample size, only exploratory statistical analyses will be performed on efficacy data collected from subjects enrolled in this combination. Details will be provided in the statistical analysis plan (SAP).

Combination 2

For Combination 2, the primary endpoint for antitumor activity is composite response rate, defined as the proportion of subjects who have objective response (confirmed per RECIST 1.1), or CTC response (CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later), or PSA decline of ≥50%, measured twice 3 to 4 weeks apart.

For subjects with biallelic DRD (cohorts 2A or 2B), the null hypothesis of ≤33% will be tested against the alternative hypothesis that the composite response rate is ≥62%. Antitumor activity of niraparib and AAP will be declared if the lower bound of the 2 sided 90% exact CI for the composite response rate is >33%. With approximately 20 subjects in Cohort 2A (or 2B), it will have over 80% power such that the lower limit of the 90% CI for the composite response rate exceeds 33%.

For subjects with monoallelic DRD (cohort 2C or 2D), the null hypothesis of ≤28% will be tested against the alternative hypothesis that the composite response rate is ≥57%. Antitumor activity of niraparib and AAP will be declared if the lower bound of the 2 sided 90% exact CI for the composite response rate is >28%. With approximately 20 subjects in Cohorts 2C (or 2D), it will have over 80% power such that the lower limit of the 90% CI for the composite response rate exceeds 28%.

With Combination 2 closed under Amendment 4 prior to reaching the originally proposed sample size, only exploratory statistical analyses will be performed on data collected from subjects enrolled in this combination. Details will be provided in the SAP.

Combination 3

In total, approximately 68 subjects will be enrolled into Combination 3. Approximately 34 subjects (17 subjects per treatment arm) will be randomized into Cohort 1 (SA niraparib+AA), and 17 subjects will be assigned to each of Cohorts 2 and 3 (non-randomized) to ensure that at least 15 PK evaluable subjects from each arm complete the study.

The primary PK parameters for statistical analysis will be C_{max} and $AUC_{0\text{-}168h}$ of niraparib and AA. An analysis of variance model (ANOVA) with treatment as fixed effect will be applied to the log-transformed PK parameters data. The differences in means between the test formulations and the reference as well as the associated 90% CIs for the differences will be constructed from the model. The results will be back-transformed to derive the GMRs and the 90% CIs of abiraterone and niraparib, respectively.

An interim PK analysis will be conducted after 8 PK evaluable subjects from each treatment group (N=16) complete PK assessments over 168 hours.

TIME AND EVENTS SCHEDULE 1: STUDY PROCEDURES AND ASSESSMENTS FOR COMBINATION 1 (NIRAPARIB AND CETRELIMAB) (TO BE REPLACED BY THE MODIFIED SCHEDULE OF EVENTS PROVIDED IN Attachment 5 ONCE AMENDMENT 6 IS APPROVED)

Phase	**Prescreening**	**Screening**	**Treatment**									**Follow-up**
CYCLE (treatment cycle is defined as 28 days)	Prior to the Screening Phase[a]	Within 28 days of Cycle 1 Day 1 unless otherwise specified	Cycle 1		Cycle 2		Cycle 3	Cycles 4 to 12	Cycle 13 and Beyond		EoT visit (within 30 days of last dose)[b]	Every 3 months
									Every Cycle	Every Other Cycle		
CYCLE DAY			1	15	1	15	1	1	1	1		
Visit Window				(±3 days)					(±3 days)		(±5 days)	(±2 weeks)
Prescreening/ Screening Informed consent[c]	X											
Biomarker panel for eligibility[d]	X											
Prescreening SAEs and deaths[e]	X											
Fresh biopsy[f]		X		X							X	
Archival tumor sample[g]		X										
Inclusion/exclusion criteria	X	X										
Demographics	X	X										
Medical history	X[h]	X										
Whole blood for cytogenetics		X										
ECG (12-lead)		X										
Screening laboratory tests (central)[i]		X										
Cetrelimab infusion (480 mg once every 4 weeks)			X		X		X	X	X			
Dispense niraparib			X		X		X	X	X			
Treatment compliance			X		X		X	X	X		X	
ECOG PS		X	X		X		X	X		X	X	
Physical examination[j]		X	X		X		X	X	X		X	
Vital signs (blood pressure, temperature, heart rate)		X	X	X	X		X	X	X			
Clinical safety laboratory tests (central or local)[k]			X	X	X	X	X	X	X		X	
Serum PSA (central)		X	X		X		X	X		X		
CT or MRI; Bone scan (^{99m}Tc)[l]		X	*From Cycle 1 Day 1, imaging will be performed every 8 weeks for the first 6*								X	X

Phase	Prescreening	Screening	Treatment											Follow-up
CYCLE (treatment cycle is defined as 28 days)	Prior to the Screening Phase[a]	Within 28 days of Cycle 1 Day 1 unless otherwise specified	Cycle 1		Cycle 2		Cycle 3	Cycles 4 to 12	Cycle 13 and Beyond		EoT visit (within 30 days of last dose)[b]	Every 3 months
									Every Cycle	Every Other Cycle		
CYCLE DAY			1	15	1	15	1	1	1	1		
Visit Window				(±3 days)					(±3 days)		(±5 days)	(±2 weeks)
			months and then every 12 weeks thereafter.									
PK sampling			*See Time and Event Schedule 2 for PK sampling times*									
Immunogenicity blood sample			*See Time and Event Schedule 2 for Immunogenicity sampling times*									
Circulating Tumor Cells[m]		X			X		X	X				X	
Whole blood for Immunophenotyping (flow cytometry)[n]			X	X	X		X						
Plasma for ctDNA analysis		X					X					X	
Whole blood for TCR sequencing and RNA analysis; reference for tumor sequencing (screening only)		X					X						
Whole blood for circulating mRNA analysis		X					X					X	
Serum for cytokine analysis[o]		X					X						
Survival Status	*Collected continuously from signing the ICF (including during the Follow up Phase)*												
AEs/SAEs and concomitant medications		*Collected from signing the ICF until 100 days after last dose of both study drugs unless the subject receives subsequent therapy, has died, is lost to follow up, or withdraws consent. See Section 12.3.1, for further information.*											
NSAIDs and antibiotics	*Collected from 30 days prior to Screening until the EoT visit*												
Related AEs/SAEs (including diagnosis of MDS/AML) and associated concomitant medications		*Collected from signing the ICF until resolution*											

AE=adverse event; AML=acute myeloid leukemia; CT=computed tomography; ctDNA=circulating tumor DNA; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EoT=end-of-treatment; eCRF=electronic case report form; ICF=informed consent form; MDS=myelodysplastic syndrome; MRI=magnetic resonance imaging; NSAIDs=non-steroidal anti-inflammatory drugs; PK=pharmacokinetics; PSA=prostate-specific antigen; RNA=ribonucleic acid; mRNA=mitochondrial ribonucleic acid; SAE=serious adverse event; ^{99m}Tc=technetium-99m; TCR=T-cell receptor

a. **Screening Phase Entry:** Subjects should enter the Screening Phase within 6 weeks of receiving a final DRD and CDK12 status result.

b. **EoT Visit:** The EoT visit must be scheduled within 30 days after both study drugs are discontinued, or prior to administration of a new anti-prostate cancer therapy, whichever occurs first.
c. **Prescreening/ Screening Informed consent**: Must be signed before first study-related activity.
d. **Biomarker panel for eligibility**: Part 1 subjects can be dosed prior to assay results; however, biomarker results are required prior to dosing for Part 2 (see Section 9.5). All subjects must have a blood sample collected to determine biomarker status using the sponsor's assay, unless already eligible by a sponsor-approved assay and reviewed by the sponsor (Tissue may also be used to determine eligibility as described in Section 9.5).
e. **Prescreening SAEs:** should only be collected if related to study procedures (e.g. blood collection)
f. **Fresh biopsy**: The screening visit biopsy is mandatory for all subjects and can be performed up to 56 days before Cycle 1 Day 1 provided no active treatment was initiated during this time. Every effort should be made to obtain fresh biopsies at Cycle 1 Day 15 and EoT (if clinically feasible) (see Section 9.5.1).
g. **Archival tumor sample:** The archival tumor sample may be collected during Cycle 1 if not collected at screening.
h. **Medical History:** Medical history obtained during the Prescreeing Phase will be disease-specific only.
i. **Screening laboratory tests**: To be performed by the central laboratory (see Table 10). Central laboratory testing may also be performed more frequently throughout the study as clinically indicated. Evaluations can be used for the Cycle 1 Day 1 assessments if performed within 14 days of Cycle 1 Day 1.
j. **Physical examination:** At screening, a full physical examination should be performed. During the Treatment Phase and at the EoT visit, limited symptom-directed physical examination will be performed. Only clinically relevant abnormalities should be recorded as AEs in the eCRF.
k. **Clinical safety laboratory tests**: To be performed by the central or local laboratory (see Table 11). During Cycle 1, complete blood counts should be performed weekly. Any subject with Grade ≥3 hematologic toxicity should also have their CBCs monitored weekly until resolution. All tests may also be performed more frequently throughout the study as clinically indicated. Prior to infusion with cetrelimab, results for a subset of tests should be available to ensure retreatment criteria are met, as per the guidelines in Section 6.2.1.2.1. Clinical safety laboratory tests should be done every 2 weeks for the first 2 cycles and then on Day 1 of every cycle thereafter (or more frequently at the investigator's discretion).
l. **CT or MRI; Bone scan (^{99m}Tc)**: Chest, abdomen, and pelvis CT or MRI scans and whole-body bone scans (^{99m}Tc) must be evaluated at screening. Scans performed ≤8 weeks of Cycle 1 Day 1 are allowed and may serve as screening scans. Subjects may have imaging performed within ±7 days of visits requiring images. Scans performed ≤6 weeks prior to the EoT visit may serve as EoT scans. Details regarding collection of scans are provided in Section 9.2. If a subject has documented radiographic progression during the Treatment Phase, additional radiographic assessments are not required during the Follow-up Phase.
m. **Circulating tumor cells**: Subsequent sample collection is required only if CTC is ≥1 at screening.
n. **Whole blood for immunophenotyping**: An additional blood collection will occur at Cycle 1 Day 8 for selected subjects in Part 1 of the study.
o. **Serum for Cytokine Analysis**: samples will be collected as indicated, but may also be collected at unscheduled visits, if deemed necessary by the investigator.

TIME AND EVENTS SCHEDULE 2: PHARMACOKINETICS AND IMMUNOGENICITY ASSESSMENTS FOR COMBINATION 1 (NIRAPARIB AND CETRELIMAB)- OBSOLETE: ASSESSMENTS ARE NO LONGER BEING PERFORMED AS OF AMENDMENT 6.

				Cetrelimab 480 mg Once Every 4 weeks			Niraparib 200 mg PO daily[a]
Cycle	**Day[b]**	**Timepoint[c]**	**Window**	**PK Part 1**	**PK Part 2**	**ImG Part 1&2**	**PK Part 1&2**
Cycle 1	Day 1	Pre-infusion/pre-dose[d]		X	X	X	X
		Cetrelimab EOI	+60min	X	X		
		Niraparib (0.5-2h)					X
		Niraparib (2.5-6h)					X
		Cetrelimab EOI+2h	±15min	X			
		Cetrelimab EOI+6h	±60min	X			
	Day 2	Relative to Day 1 EOI	within 8h	X			
	Day 4	Relative to Day 1 EOI	±1 day	X			
	Day 8	Relative to Day 1 EOI	± 1day	X	X		
	Day 15[e]	Relative to Day 1 EOI	±2 days	X	X		
Cycle 2	Day 1	Pre-infusion/pre-dose[d]	-2h	X	X	X	X
		Cetrelimab EOI	±15min	X	X		
		Niraparib (0.5-2h)					X
		Niraparib (2.5-6h)					X
	Day 15[e]	Relative to Day 1 EOI	±2 days	X	X		
Cycle 3 to 4	Day 1	Pre-infusion/pre-dose[d]	-2h	X	X	X	
		Cetrelimab EOI	±15min	X	X		
Cycle 5	Day 1	Pre-infusion[d]		X	X	X	
		Cetrelimab EOI	+60min	X	X		
		Cetrelimab EOI+2h	±15min	X			
		Cetrelimab EOI+6h	±60min	X			

				Cetrelimab 480 mg Once Every 4 weeks			Niraparib 200 mg PO daily[a]
Cycle	**Day[b]**	**Timepoint[c]**	**Window**	**PK Part 1**	**PK Part 2**	**ImG Part 1&2**	**PK Part 1&2**
Cycle 6	Day 1	Pre-infusion/pre-dose[d]	-2h	X	X	X	X
		Cetrelimab EOI	±15min	X	X		
Cycle 12	Day 1	Pre-infusion/pre-dose[d]	-2h		X	X	X
		Cetrelimab EOI	±15min		X		
End of Treatment[f]				X	X	X	
Follow-up				X	X	X	

EOI=end of infusion; h=hour; ImG=immunogenicity sampling; min=minutes; PK=pharmacokinetics sampling; PO=orally (taken by mouth)
NOTE: 2 dose regimens for cetrelimab will be explored in Part 1. Once a dose regimen is chosen, subjects on the unselected regimen will be switched to the selected regimen and will follow the corresponding Part 2 PK sampling schedule.

a. Niraparib is dosed within 0.5 hours before the start of infusion of cetrelimab. The subject must not take niraparib at home in the morning on PK/immunogenicity sampling days; both study drugs should be administered at the investigational site.
b. If dose delay occurs, then samples should be collected on the actual day of drug administration, not on the originally scheduled administration day.
c. Timepoints are relative to the dosing of niraparib and PK samples may be collected during the cetrelimab infusion, if necessary; however, the sample should be drawn from the contralateral arm opposite the cetrelimab infusion.
d. Pre-infusion PK and immunogenicity samples for cetrelimab should be collected up to 2 hours before the start of cetrelimab infusion.
e. To be performed if subject is coming to clinic for safety labs.
f. The EoT visit must be scheduled within 30 days after both study drugs are discontinued, or prior to administration of a new anti-prostate cancer therapy, whichever occurs first.

TIME AND EVENTS SCHEDULE 3: STUDY PROCEDURES AND ASSESSMENTS FOR COMBINATION 2 (NIRAPARIB AND AAP) (TO BE REPLACED BY THE MODIFIED SCHEDULE OF EVENTS PROVIDED IN Attachment 5 ONCE AMENDMENT 4 IS APPROVED)

PHASE	Prescreening	Screening	Treatment											Follow-up
CYCLE (treatment cycle is defined as 28 days)	Prior to the Screening Phase[a]	Within 28 days of Cycle 1 Day 1 unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycles 4 to 7	Cycle 8 to 12 Every cycle	Cycle 13 and Beyond Every 2 Cycles (eg, Cycles 13, 15, 17)	EoT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY			1	15	1	15	1	15	1	1	1		
VISIT WINDOW			(±3 days)							(±3 days)		(+5 days)	(±2 weeks)
Informed consent[c]	X												
Biomarker panel for eligibility	X												
Prescreening SAEs and deaths[d]	X												
Archival tumor sample[e]		X											
Inclusion/exclusion criteria	X	X											
Demographics	X	X											
Medical history	X[f]	X											
Whole blood for cytogenetics		X											
ECG, 12-lead		X											
Screening laboratory tests (central)		X											
Dispense study drugs			X		X		X		X	X	X		
Treatment compliance					X		X		X	X	X	X	

PHASE	Prescreening	Screening	Treatment										Follow-up
CYCLE (treatment cycle is defined as 28 days)	Prior to the Screening Phase[a]	Within 28 days of Cycle 1 Day 1 unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycles 4 to 7	Cycle 8 to 12 Every cycle	Cycle 13 and Beyond Every 2 Cycles (eg, Cycles 13, 15, 17)	EoT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY			1	15	1	15	1	15	1	1	1		
VISIT WINDOW				(±3 days)						(±3 days)		(+5 days)	(±2 weeks)
ECOG PS		X	X		X		X		X	X	X	X	
Physical examination[g]		X	X		X		X		X	X	X	X	
Vital signs (blood pressure, heart rate)		X	X		X		X		X	X	X	X	
Clinical safety laboratory tests[h] (central or local)			X (weekly)		X	X	X	X	X	X	X	X	
Serum PSA (central)		X	X		X		X		X	X	X	X	
CT or MRI; Bone scan (^{99m}Tc)[i]		X	*From Cycle 1 Day 1, imaging will be performed every 8 weeks for the first 6 months and then every 12 weeks thereafter.*									X	X
Circulating tumor cells[j]		X			X		X		X			X	
Survival Status	*Collected continuously from signing the ICF (including during the Follow up Phase)*												
AEs/SAEs and concomitant medications		*Collected continuously from signing the ICF until 30 days after last dose of study drugs unless the subject receives subsequent therapy, has died, is lost to follow up, or withdraws consent. See Section 12.3.1, for further information.*											
Related AEs/SAEs and associated	*Collected continuously from signing the ICF until resolution*												

PHASE	Prescreening	Screening	Treatment										Follow-up
CYCLE (treatment cycle is defined as 28 days)	Prior to the Screening Phase[a]	Within 28 days of Cycle 1 Day 1 unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycles 4 to 7	Cycle 8 to 12 Every cycle	Cycle 13 and Beyond Every 2 Cycles (eg, Cycles 13, 15, 17)	EoT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY			1	15	1	15	1	15	1	1	1		
VISIT WINDOW				(±3 days)						(±3 days)		(+5 days)	(±2 weeks)
concomitant medications													

AE=adverse event; con meds=concomitant medications; CT=computed tomography; CTC=circulating tumor cells; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EoT=end-of-treatment; ICF=informed consent form; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; RNA=ribonucleic acid; SAE=serious adverse event; SSE=symptomatic skeletal event; ^{99m}Tc=technetium-99m;

a. **Screening Phase Entry:** Subjects should enter the Screening Phase within 6 weeks of receiving a final DRD status result.
b. **EoT Visit:** The EoT visit must be scheduled within 30 days after study drugs are discontinued, or prior to administration of a new anti-prostate cancer therapy, whichever occurs first.
c. **Informed consent:** Must be signed before first study-related activity.
d. **Prescreening SAEs:** should only be collected if related to study procedures (e.g. blood collection)
e. **Archival tumor sample:** The archival tumor sample may be collected during Cycle 1, if not collected at screening.
f. **Medical History:** Medical history obtained during the Prescreening Phase will be specific to prior prostate cancer-related therapies and procedures (eg, prostatectomy, radiation, past chemotherapy).
g. **Physical examination:** At screening, a full physical examination should be performed. During the Treatment Phase and at the EoT visit, limited symptom-directed physical examination will be performed. Clinically relevant abnormalities should be recorded as AEs in the eCRF.
h. **Clinical safety laboratory tests:** During Cycle 1, complete blood counts should be performed weekly. For the first 3 cycles, liver function tests will be collected every 2 weeks (ie, on Day 1 and Day 15).
i. **CT or MRI; Bone scan:** Chest, abdomen, and pelvis CT or MRI scans and whole-body bone scans (99mTc) must be evaluated at screening. Scans performed ≤8 weeks of Cycle 1 Day 1 are allowed and may serve as screening scans. Subjects may have imaging performed within ±7 days of visits requiring images.
j. **Circulating tumor cells:** If CTC is ≥1 at screening, subsequent sample collection at cycles 2, 3, 5, 7, and EoT only.

THE TIME AND EVENTS SCHEDULE FOR COMBINATION 3 (NIRAPARIB/ABIRATERONE ACETATE FIXED DOSE COMBINATION) IS IN Attachment 6

ABBREVIATIONS

^{99m}Tc	technetium-99m
AA	abiraterone acetate
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the curve
BA	bioavailability
BM	biomarker
BRCA	breast cancer gene
CBC	complete blood count
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMV	cytomegalovirus
CR	complete response
CRPC	castration-resistant prostate cancer
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cells
ctDNA	circulating tumor DNA
DLT	Dose-limiting toxicity
DNA	deoxyribonucleic acid
DP	drug product
DRC	Data Review Committee
DRD	DNA-repair gene defects
DSB	double-stranded breaks
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EoT	end-of-treatment
FIH	first-in-human
FOIA	Freedom of Information Act
GCP	good clinical practice
GLP	good laboratory practice
GnRHa	gonadotropin releasing hormone analogue
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRR	homologous recombination repair
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
irAE	immune-related adverse event
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IWRS	interactive web response system
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events

NFAT	nuclear factor of activated T-cells
ORR	objective response rate
OS	overall survival
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PBMC	peripheral blood mononuclear cell
PCWG3	Prostate Cancer Working Group 3
PFS	progression-free survival
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
RR	response rate
SAC	safety assessment committee
SAE	serious adverse event
SAP	statistical analysis plan
SIPPM	site investigational product preparation manual
SSE	symptomatic skeletal event
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

Niraparib is an orally available, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, with potent activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases.[28] The sponsor licensed niraparib for the development of prostate cancer from TESARO, who is currently conducting clinical studies of breast cancer (IND 117580), ovarian cancer (IND 100996) and non-small cell lung cancer (134426). Niraparib was approved in the United States (US) by the Food and Drug Administration (FDA) on 27 March 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Niraparib also received European Commission approval (16 November 2017) for use as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy (EMA/CHMP/574018/2017).

In this study, the sponsor intends to investigate niraparib in combination with other agents (hereafter, the combination of niraparib and other anticancer agent will be termed "niraparib combination therapies" and the other anticancer agent will be termed "combination agent") for the treatment of metastatic castration-resistant prostate cancer (mCRPC). This protocol will describe the overall conduct of the study, which will investigate Combination 1 (niraparib in combination with cetrelimab [JNJ-63723283]), Combination 2 (niraparib in combination with ZYTIGA® [abiraterone acetate] plus prednisone; hereafter referred to as AAP), and Combination 3 (a relative bioavailability [BA] evaluation of fixed-dose combination [FDC] tablets of niraparib plus AA versus niraparib plus AA administered as single agents) for the treatment of mCRPC. The sponsor may amend this protocol in future to investigate additional niraparib combinations, if and when scientific data are available to support such studies.

Cetrelimab is a fully human immunoglobulin (Ig) G4 kappa monoclonal antibody (mAb) that binds to PD-1 with high affinity and specificity. It blocks binding to both PD-1 ligand 1 (PD-L1) and PD-1 ligand 2 (PD-L2) to enhance pro-inflammatory cytokine production. Cetrelimab is currently being investigated in a Phase 1-2, first-in-human (FIH) study in subjects with advanced cancers.

Abiraterone acetate [AA; JNJ-212082] is a pro-drug of abiraterone (JNJ-589485) 17-(3-pyridyl) androsta-5,16-dien-3β-ol], an androgen biosynthesis inhibitor. Abiraterone selectively inhibits the enzyme CYP17, which is found in the testes and adrenals, as well as in prostate tissues and tumors.[38] The clinical benefits of AAP for the treatment of prostate cancer were demonstrated in 3 large, randomized, double-blind, placebo-controlled Phase 3 studies. These studies included patients with metastatic castration-resistant prostate cancer (mCRPC) post-chemotherapy (COU-AA-301), chemotherapy-naïve patients (Study COU-AA-302), and patients with high-risk metastatic hormone-naïve (mHNPC) disease (Study 212082PCR3011).[9,13,42,46] AAP is currently approved in more than 100 countries worldwide for the treatment of men with metastatic prostate cancer (exact wording of indications vary by region).[37]

Two FDC drug products, FDC1 and FDC2, will be evaluated. The FDC drug product formulations will be manufactured as immediate-release film-coated 50 mg niraparib/500 mg AA (FDC1 low strength (G009) and FDC2 low strength (G014) or 100 mg niraparib/500 mg AA (FDC1 regular

strength (G010 and FDC2 regular strength (G012) tablets for oral administration containing 79.70 mg or 159.40 mg of niraparib tosylate monohydrate drug substance, equivalent to 50 or 100 mg niraparib free base, and 500 mg of AA drug substance.

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.

1.1. Background and Design Rationale

PARP inhibitors are currently being investigated alone and in various combination regimens for the treatment of patients with prostate cancer. However, it is unclear if PARP inhibitors have an effect on all prostate tumors, or just a subset with DNA-repair gene defects (DRD). Patients with metastatic castration-resistant prostate cancer (mCRPC) and DRD (ie, biomarker positive [BM+] patients) may have an improved response to single-agent PARP inhibitors compared with patients without DNA-repair anomalies (ie, biomarker-negative [BM-] patients).[35]

The mechanism by which this is thought to occur has been well established. In response to genotoxic insult, tumor cells recruit proteins, such as PARPs, to promote DNA-repair, which allows tumor cells to survive. PARP inhibition leads to an accumulation of unrepaired single-strand breaks, which result in stalling and collapse of replication forks and, consequently, to double-strand breaks (DSBs). One way of repairing DSBs is through homologous recombination repair (HRR), a type of DNA repair. If not repaired, DSBs result in cell death. When tumor cells with DRD involving the HRR pathway (eg, breast cancer genes [BRCA]1/2) are treated with a PARP inhibitor, they are unable to efficiently and accurately repair DSBs, which creates a synthetic lethal condition.[6,11,51] In patients with mCRPC, DNA-repair anomalies are identified in approximately 20% to 30% of tumors.[17,45]

Clinical data from the TOPARP study with the PARP inhibitor, olaparib (Lynparza®), have demonstrated potential efficacy in subjects with mCRPC whose tumors have DRD following treatment with chemotherapy and androgen receptor (AR)-targeted agents.[35] Initial data suggest improvement in both radiographic progression-free survival (rPFS) and overall survival (OS) in olaparib-treated subjects with either germline or somatic DRD (ie, subjects with BM+ tumors containing defects in genes such as BRCA1, BRCA2, ATM, and FANCA, n 16) compared with those subjects whose tumors did not have germline or somatic mutations or deletions (ie, BM- subjects, n 34). In this study, rPFS was longer for those subjects whose tumors were BM+ compared with subjects whose tumors were BM- (median 9.8 months versus 2.7 months, respectively). Though preliminary, OS data showed a similar trend (13.8 months versus 7.5 months); however, these findings are difficult to interpret given the small sample size (16 BM+ subjects) and retrospective biomarker analysis. Out of 32 subjects with measurable disease, 6 subjects had confirmed radiologic partial response (19%). Of the BM+ subjects in this subset, 5 out of 7 subjects had a confirmed radiologic partial response. In the TOPARP study, prostate cancer subjects who were BM- appeared to have no significant response to treatment with olaparib.

The sponsor is currently investigating the efficacy and safety of single-agent 300 mg niraparib in subjects with mCRPC and DRD in an ongoing Phase 2 study (64091742PCR2001). The sponsor also explored the safety and antitumor activity of niraparib doses of 200 and 300 mg in

combination with 1,000 mg abiraterone acetate plus 10 mg prednisone daily in subjects with or without DNA-repair anomalies in the completed Phase 1b study (64091742PCR1001). This study established the RP2D of niraparib in combination with AR-targeted therapy as niraparib 200 mg plus AA 1,000 mg and prednisone 10 mg daily.[47]

Therapeutic strategies that combine other anticancer agents to create a synthetical lethal environment are necessary to expand the cohort of patients who could benefit from treatment with PARP inhibitors (ie, those without DRD), as well as improve the response of patients whose tumors exhibit DRD. PARP inhibitors may be an important backbone therapy for the treatment of prostate cancer with DRD. However, the exploration of different PARP inhibitor combination strategies as separate clinical studies would be logistically difficult, time consuming, and delay promising therapies from reaching patients in need. The rapid implementation of new research findings within the protocol framework and study design is essential.[4] Protocols that allow multiple arms with different treatment combinations are increasingly being utilized to efficiently evaluate multiple therapies for a particular disease type and have been shown to be substantially more efficient than traditional study designs.[58,61]

Once efficacy analyses (if applicable) have been performed for each combination, those combinations can be evaluated if further study is warranted. This strategy significantly reduces time, number of subjects, and the cost needed to bring promising agents to the clinical setting. Therefore, the sponsor has designed this protocol to efficiently evaluate niraparib in combination with other anticancer agents as a treatment for prostate cancer, in an effort to help the greatest number of patients in need.

1.1.1. Combination 1: Niraparib and Cetrelimab

The sponsor intends to investigate niraparib in combination with an anti-PD-1 mAb checkpoint inhibitor, cetrelimab. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.[59] The normal function of PD-1 is to suppress unwanted or excessive immune responses, including autoimmune reactions. PD-1 is typically expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, regulatory T-cells, and natural killer cells. PD-1 is an Ig superfamily member that negatively regulates antigen-receptor signaling upon binding to its ligands, PD-L1 and PD-L2. PD-1 is a transmembrane glycoprotein with an Ig variable-type ligand binding domain and a cytoplasmic tail responsible for binding to signaling molecules.[30] Following T-cell stimulation, PD-1 signaling is induced, causing dephosphorylation of effector molecules involved in the CD3 T-cell signaling cascade.

The investigation of checkpoint inhibitors in prostate cancer is ongoing and some treatments have shown some antitumor activity, albeit in very few subjects to date. In a Phase 1-2 study of the CTLA-4 inhibitor, ipilimumab, in 28 tumor-evaluable subjects, 1 had a complete response (CR) and 2 had unconfirmed partial response (PR).[53] In a Phase 1 study of the anti-PD-1 mAb, pembrolizumab, 2 out of 3 evaluable subjects had a PR to single-agent therapy.[16] Though these data are encouraging, the optimal setting and patient population for treatment with these agents has not been established.

Cetrelimab is a fully human IgG4 kappa anti-PD-1 mAb. Cetrelimab binds to PD-1 with high affinity and specificity, blocks binding to both PD-L1 and PD-L2 ligands, enhances pro-inflammatory cytokine production from ex vivo stimulated T-cells, and reduces tumor volume in human PD-1 knock-in mice bearing MC38 murine colon carcinoma tumors. Cetrelimab is currently being investigated in an FIH proof-of-concept study (Study 63723283LUC1001).

The rationale for combining a PARP inhibitor and a checkpoint inhibitor has a robust preclinical foundation. In cell lines and animal models unselected for DRD, PARP inhibitors were associated with upregulation of PD-L1 expression. Once treated with PD-L1 blockade, these cells became sensitive to T-cell killing.[26] In addition, tumor associated antigens are thought to be released by PARP inhibitors and are hypothesized to potentiate the efficacy of checkpoint inhibitors. The combination of the PARP inhibitor, niraparib, and the PD-1 inhibitor, cetrelimab, has the potential to benefit patients with mCRPC who may or may not have DRD or CDK12 pathogenic alterations.

Niraparib is being investigated by TESARO in combination with the anti-PD-1 mAb, pembrolizumab, for the treatment of recurrent, platinum-resistant ovarian cancer and triple-negative breast cancer (Phase 1/2 TOPACIO study) in biomarker-unselected subjects. In the dose escalation phase, a disease control rate of 69% was observed (9 of 13 evaluable subjects), including 3 PRs and 1 CR, in subjects with platinum-resistant ovarian cancer. With a dose of niraparib at 200 mg once daily, 1 of 7 subjects enrolled in Phase 1 of the study was reported with dose-limiting toxicities (DLTs; Grade 3 anemia, Grade 4 neutropenia, and Grade 4 thrombocytopenia). At Dose Level 2, 1 of 7 subjects was reported with 1 DLT of Grade 4 thrombocytopenia. No significant overlapping toxicities were observed. The 200-mg dose was established as the RP2D for combination studies with niraparib. However, patients who meet certain hematologic parameters after at least 2 cycles of therapy are permitted to escalate to niraparib 300 mg once daily on or after Cycle 3 Day 1, in an effort to potentially increase efficacy with the higher dose of niraparib. As of August 2017, 2 subjects have been escalated from 200 mg to 300 mg niraparib after 2 cycles and have had no Grade ≥3 events. Data from 83 subjects treated to date show no new safety signals with the combination. Thirty subjects (36%) enrolled in Phase 2 of the study reported treatment-related Grade ≥3 AEs that have been primarily hematologic (anemia, thrombocytopenia, and fatigue). Preliminary data for antitumor activity are encouraging with 6 of 29 subjects with ovarian cancer and 5 of 27 subjects with breast cancer showing at least a PR by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Notably, responses have been observed in subjects with BRCA-wild-type and PD-L1 negative tumors in both ovarian and triple-negative breast cancers.[32]

In the mCRPC setting, Karzai et al have shown that olaparib plus the anti-PD-L1 checkpoint inhibitor, durvalumab, showed signals of efficacy in subjects with mCRPC who were unselected for DRD.[29] Out of 16 subjects that were on the study for greater than 2 months, 7 had prostate-specific antigen (PSA) declines of >50%, the 9-month progression-free survival (PFS) rate was 57.8%, and median PFS was not yet reached.[1] AEs were generally manageable and Grade 3/4 AEs included anemia (21%), thrombocytopenia (7%), neutropenia (7%), nausea (7%), and fatigue (7%). Data on radiographic response rate are not yet available.

The olaparib PROfound study showed that mCRPC patients who had CDK12 gene alterations treated with olaparib had a median rPFS of 5.09 months compared to an rPFS of 2.20 months on either abiraterone or enzalutamide, demonstrating that patients with CDK12 gene alterations achieved greater benefit from a PARP inhibitor compared to antiandrogen agents.[8] Furthermore, Antonarakis et al. concluded that a proportion of these patients respond modestly to PD-1 inhibitors, potentially implicating CDK12 deficiency in immunotherapy responsiveness.[3] Because CDK12 appears to define a distinctly immunogenic class of prostate cancer and also now that there is randomized clinical trial evidence that PARP inhibition confers a rPFS advantage versus standard of care hormonal therapy, the combination of these two independent mechanisms of action is expected to confer at least additive clinical benefit to the proposed eligible population.

1.1.2. Combination 2: Niraparib and AAP

The sponsor will investigate niraparib in combination with AAP. In addition to facilitating DNA-repair, dual roles for PARP in supporting AR activity have been observed in the preclinical setting. PARP-1 is a potent modulator of both AR function and response to DNA damage.[51] Primary human prostate tumor ex vivo cultures showed significant antitumor response to PARP inhibition, which was correlated with diminished AR activity. Similarly, RNA-seq analysis showed that AR regulated transcription of genes involved in DNA-repair in LNCaP cells after androgen treatment.[40] The impact of niraparib in combination with abiraterone was evaluated by the sponsor in the human VCaP-prostate tumor model. Mice bearing VCaP tumors were treated with niraparib either alone, or in combination with abiraterone. The combination of niraparib plus abiraterone showed better inhibition of tumor growth and survival prolongation than the single agents (sponsor data). This result further supports the hypothesis that combining a PARP inhibitor with AA may benefit prostate cancer patients.

In the clinical setting, recent data have shown the efficacy of combining AR-targeted therapy and a PARP inhibitor in patients with metastatic prostate cancer, but the patient population most sensitive to this combination is not yet known. Patients treated with a combination of olaparib and AAP had improved rPFS compared with those treated with AAP alone.[7] This benefit was seen in patients with and without DRD. A study of patients treated with the combination of veliparib and AAP showed benefit only in tumors that were DRD positive.[21] Patients whose tumors have DRD may have different responses based on the type of mutation and gene type (e.g. monoallelic vs. biallelic, BRCA vs. other). Therefore, further exploration of the efficacy of the AAP plus PARP inhibitor combination based on the mutation and gene type is warranted.

In Study 64091742PCR1001 the sponsor evaluated niraparib in combination with AAP. Niraparib 200 mg was selected to be the optimal dose to be combined with AAP. The combination of 200 mg niraparib+1,000 mg AA and 10 mg prednisone daily is also being evaluated in the ongoing Phase 3, double-blind, randomized, placebo-controlled Study 64091742PCR3001 (MAGNITUDE). Study 64091742PCR3001 is intended to be the pivotal clinical study supporting registration of niraparib in combination with AAP for the treatment of men with mCRPC (with and without DRD).

1.1.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

In parallel to Study 64091742PCR3001, as mentioned above, the Sponsor is pursuing development of an FDC tablet formulation of niraparib and AA with the aim of simplifying the combination regimen by reducing the pill burden. Based on the recommended dose of AA and the recommended Phase 2 dose for niraparib under Study 64091742PCR1001, the combination of these 2 individual products would require patients to be treated with up to 6 pills per day with the further addition of 1 to 2 tablets of prednisone or prednisolone. The FDC tablet presentation would reduce the number of pills to 2 tablets per day. Reducing the pill burden for patients on oral medications for cancer may improve compliance as cancer patients often take multiple oral medications for cancer and for other comorbid conditions.[15]

The MAGNITUDE Study is a randomized, placebo-controlled, double-blind study investigating niraparib and AAP versus AAP and placebo as first-line therapy for subjects with mCRPC. The study stratifies subjects into 2 cohorts; those with HRR gene alterations (Cohort 1, n 400 planned to be enrolled) and those with no HRR gene alterations (Cohort 2, n 600 planned to be enrolled). Cohort 3 is an open-label cohort to evaluate the clinical efficacy and safety of the FDC tablet formulation of niraparib and AA in subjects with HRR gene alterations. This cohort is expected to enroll approximately 40 subjects (approximately 20 with BRCA alterations); enrollment will begin after enrollment into Cohorts 1 and 2 have completed and when the sponsor opens Cohort 3 for enrollment.

Data from a futility analysis of the cohort without HRR gene alterations (Cohort 2) was reviewed by an Independent Data Monitoring Committee (IDMC) on 13 August 2020. A total of 233 subjects were included in the analysis, 117 in the niraparib and AAP arm and 116 in the AAP arm. Baseline demographics, disease characteristics and prior treatments were generally balanced across treatment groups. The IDMC determined that the futility rule was met, indicating the study did not show additional benefit of adding niraparib to AAP in subjects with no HRR gene alterations. No new safety signals were identified. Based on the IDMC recommendation, and after review by the Sponsor Committee, further enrollment into Cohort 2 was not re-opened. Subjects in Cohort 2 may remain on AAP, niraparib, or both. The MAGNITUDE study remains open to complete enrollment into Cohort 1 and Cohort 3 in subjects with HRR gene alterations.

In Combination 3, the sponsor will evaluate the relative BA of 2 regular-strength and 1 low-strength FDC tablet formulations of niraparib plus AA compared to coadministration of single agents (SA) of the available commercial formulations of niraparib capsules and AA tablets

in subjects with mCRPC. The objective of evaluating Combination 3 in this platform protocol is to determine the relative BA of the FDC formulations and select the 1 with favorable PK parameters for further clinical development. Thus, FDC tablets will be given only as a single dose for the purpose of assessing relative BA. Subjects will be dosed with single agents, as in Combination 2, for the remainder of their treatment after the PK assessment is complete. The design and procedures associated with Combination 3 are fully described in Attachment 6. Cross-references and links back to the protocol have been made for general study-related information (eg, background, administrative requirements).

It is expected that the 2 formulations of the regular-strength FDC tablets (2x100 mg niraparib/500 mg AA), ie, FDC1 (G010) and FDC 2 (G012), would result in similar exposures of niraparib and abiraterone when compared to the SAs. See Section 14.1, for a physical description of the FDC study drugs. The sponsor also developed 2 low-strength versions of the FDC tablet formulations, FDC1 (G009) and FDC2 (G014). Each low-strength FDC tablet formulation has 50 mg niraparib and 500 mg AA. Based on the PK results from regular-strength FDC tablets, 1 of the 2 low-strength FDC tablet formulations will be further tested to obtain additional PK information.

The rationale to develop the low-strength FDC tablet is to address the need for patients who may require a lower dosage of niraparib due to toxicity (eg, thrombocytopenia, neutropenia). Based on data from Study 64091742PCR1001, in the niraparib plus AAP treatment group, 21% of subjects with a starting niraparib dose of 200 mg had a reduction in niraparib to 100 mg, most frequently due to cytopenias, and only 5% had a dose reduction in AA. Therefore, given the low rate of dose reduction in AA, an FDC tablet formulation with a lower strength of AA is not being developed.

Due to the genotoxicity of niraparib, this relative BA of FDC will be evaluated in mCRPC patients, regardless of DRD and prior line of therapy, but not in healthy volunteers. Furthermore, mCRPC is also the target population for the niraparib registration Study 64091742PCR3001.

1.2. Summary of Available Nonclinical and Clinical Data for Niraparib

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 niraparib Investigator's Brochure.[24]

Nonclinical Data

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

In toxicology studies, a dose-related (0 to 10 mg/kg) increase in mean arterial pressure and heart rate was observed following 30-minute infusion to anesthetized dogs. There were no treatment-related changes in blood flow, PR interval, or QTc interval in anesthetized dogs; however, a small increase in QRS interval was observed at the 10 mg/kg dose. The peak niraparib exposure following 10 mg/kg infusion was 4,896 ng/mL. 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 Data

Niraparib has been evaluated at various doses, alone and in combination with other anticancer agents. With increasing doses, exposures increased linearly and dose-proportionally. Doses from 100 mg per day to 400 mg per day have shown antitumor activity. The DLT at 400 mg once daily was thrombocytopenia. Niraparib is currently being investigated at 300 mg once daily as monotherapy in ongoing registration clinical studies in ovarian and breast cancer and has been approved in the US at that dose for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy.[62] The dose of 300 mg is also being evaluated as monotherapy in sponsor Study 64091742PCR2001 for the treatment of subjects with mCRPC and DRD. Doses of 200 mg and 300 mg niraparib are also being explored in various ongoing combination studies, including sponsor study 64091742PCR1001 investigating niraparib and AAP and the TESARO TOPACIO study in combination with pembrolizumab.[55]

In the Phase 3 registration NOVA study (NCT01847274) for subjects with ovarian cancer previously treated with platinum-based chemotherapy, the most common Grade 3/4 AEs were thrombocytopenia (29%), anemia (25%), and neutropenia (20%).[62] Other important risks that have been reported with the use of niraparib are hypertension, including hypertensive crisis and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).[24] Preliminary safety data obtained from the sponsor's 64091742PCR2001 single-agent study suggest a similar safety profile in subjects with mCRPC, with no new safety signals being observed to date (sponsor's internal data).

Following oral administration, niraparib is rapidly absorbed, with peak concentrations occurring at about 3 hours postdose in subjects. The absolute bioavailability in humans is approximately 73%. Niraparib can be administered with or without food. Following multiple daily doses of 300 mg niraparib, the mean half-life is 36 hours. In a population pharmacokinetic (PK) analysis, the apparent total clearance (CL/F) of niraparib was 16.2 L/h. Niraparib is cleared though renal and hepatic metabolism, both as unchanged drug and as metabolites. In humans, M1 and M10 (glucuronides of M1) are the major circulating metabolites after single-dose administration, with M1 being present at exposures comparable to or slightly higher than the parent drug. The elimination of M1 appears to be parallel to that of the parent drug.

1.3. Summary of Available Nonclinical and Clinical Data for Combination Agents

1.3.1. Combination 1: Niraparib and Cetrelimab

Cetrelimab is a fully human IgG4 kappa anti-PD-1 mAb containing the hinge-stabilizing S228P mutation. This mutation prevents the fragment antigen binding arm exchange that normally occurs with IgG4 antibodies.[2] A summary of the nonclinical and clinical information available for cetrelimab to date is provided below. For the most comprehensive nonclinical and clinical

information regarding cetrelimab, refer to the latest version of the cetrelimab Investigator's Brochure.[22]

Nonclinical Data

Nonclinical Pharmacology

PD-1 blockade with cetrelimab enhanced T-cell function in vitro, as evidenced by dose dependent increases in pro-inflammatory cytokine levels in mixed lymphocyte reaction (MLR) and cytomegalovirus (CMV) recall assays. In addition, cetrelimab reversed PD-1 mediated suppression of T-cell receptor signaling by promoting nuclear factor of activated T-cells (NFAT)-reporter transcriptional activity in Jurkat T-cell lines. The in vitro activity of cetrelimab was comparable to that observed for nivolumab and pembrolizumab analogues in the MLR, CMV, and NFAT-reporter assays. In vivo, cetrelimab also inhibited tumor growth in human PD-1 knock-in mice bearing MC38 murine colon carcinoma tumors and showed comparable antitumor efficacy to a nivolumab analogue.

Toxicology

Data from the 4- and 5-week toxicology studies in cynomolgus monkeys indicate cetrelimab was clinically well-tolerated and demonstrated evidence of pharmacology (T-cell dependent antibody response enhancement). No cetrelimab-related effects were noted in cardiovascular, respiratory, or central nervous system during the 5-week study. Primary cetrelimab-related findings noted in 4- and 5-week monkey studies at ≥10 mg/kg/wk included slight increases in monocyte counts and prothrombin times in the 4-week study, and slight increases in prothrombin times. In the 5-week study, the no-observed-adverse-effect level was 100 mg/kg/wk (mean C_{max} 3,055.75 µg/mL and $AUC_{Day29\ 36}$ 12,658.15 µg day/mL following the dose on Day 29). cetrelimab cytokine response in vitro in human blood was similar to other immune-modulatory compounds with a low risk of cytokine-release syndrome.

Clinical Data

Clinical experience with cetrelimab in humans is from an ongoing monotherapy Study 63723283LUC1001. This is a multicenter, Phase 1-2, FIH study of cetrelimab in subjects with advanced solid tumors. Part 1 of the study, initiated on 21 November 2016, consists of dose escalation cohorts and PK/pharmacodynamic cohorts. cetrelimab is being evaluated in selected solid tumor types including non-small-cell lung cancer, melanoma, bladder cancer, renal cancer, small cell lung cancer, and gastric/esophageal cancer.

As of the data cutoff date of 4 September 2017, 76 subjects have received at least 1 dose of cetrelimab. The duration of cetrelimab treatment ranged from 1 to 4 months; the number of doses administered ranged from 1 to 14. Thirteen subjects had discontinued study treatment. Eleven subjects discontinued due to progressive disease, 1 subject discontinued due to a treatment-emergent AE (TEAE) of Grade 3 pneumonitis, and 1 subject died. AEs have been consistent across tumor types following monotherapy and have not demonstrated a clear dose-response relationship. Of the 76 treated subjects, 72 (94.7%) were reported with at least 1 TEAE. The most frequently reported TEAEs (≥10% of subjects) were dyspnea (18.4%); diarrhea and

anemia (17.1% each); asthenia, fatigue, and pyrexia (14.5% each); abdominal pain, nausea, hypertension, and decreased appetite (11.8% each); and hyponatremia (10.5%).

Overall, the safety profile has been similar to that of other anti-PD1 agents (such as nivolumab and pembrolizumab), although a higher percentage of treatment-emergent infusion-related reactions have been observed to date. Eight of the 76 treated subjects were reported with treatment-emergent infusion-related reactions (IRRs) as assessed by the investigator. The most frequently reported treatment-emergent IRRs were nausea and generalized rash in 2 subjects each. Other events reported as IRRs included malaise, dyspnea, non-cardiac chest pain, tachycardia, vomiting, pyrexia, flushing, increased gamma-glutamyl transferase, an infusion reaction with no additional symptoms reported, and body itching redness were reported by 1 subject each. All subjects who were reported with IRRs received cetrelimab 240 mg once every 2 weeks, with the exception of 1 subject who received cetrelimab 460 mg once every 2 weeks and was reported with IRRs of nausea, generalized rash, tachycardia, and vomiting. The IRRs reported in the study were mostly Grade 1 or Grade 2. With the exception of increased gamma-glutamyl transferase and body itching redness, the IRRs were transient and resolved with the interruption of study treatment. None of the reported IRRs were considered serious AEs (SAEs). These data should be interpreted with caution given the relatively small number of subjects dosed to date.

As of 4 September 2017, of the 76 subjects treated with cetrelimab, 64 were evaluable for response. Five subjects, all of whom were receiving cetrelimab 240 mg once every 2 weeks and had either NSCLC, melanoma, gastric cancer, or thymoma, had a PR (2 confirmed responses) and 30 subjects (with NSCLC, melanoma, renal cell cancer, bladder cancer, gastric/esophageal cancer, or others) had stable disease. As of 5 October 2017, 9 subjects have been treated with cetrelimab 480 mg every 4 weeks. No subjects were reported with DLTs to date and the side effect profile is similar to the 240 mg every 2 weeks dose. Efficacy analyses are not yet available for those subjects treated with cetrelimab 480 mg every 4 weeks.

In 20 PK-evaluable subjects, serum concentration data following the first dose of cetrelimab exhibited approximately linear PK. Maximum serum concentration (C_{max}), minimum serum concentration after the first dose (C_{min1}), and area under the curve for 1 dosing interval (AUC_{tau}) increased in an approximately dose-proportional manner from 80 to 460 mg. Interpatient variability was generally consistent with mAb therapeutics. PD-1 receptor occupancy on circulating CD3+ T-cells was evaluated in 24 subjects and preliminary results indicated postdose saturation following 80 to 460 mg once every 2 weeks and maintenance of relative saturation throughout continued dosing in the majority of subjects.

1.3.2. Combination 2: Niraparib and AAP

AAP is approved for the treatment of patients with metastatic prostate cancer.[64] A brief summary of the clinical information available for AAP is provided below. For the most comprehensive nonclinical and clinical information regarding AAP, refer to the latest version of the abiraterone acetate Investigator's Brochure.[22]

In clinical studies of subjects with metastatic prostate cancer, the most common AEs related to AA include peripheral edema, hypokalemia, urinary tract infection, ALT increased, aspartate

aminotransferase increased, dyspepsia, hematuria, hypertension, and fractures.[13,64] AA should be used with caution in subjects with a history of cardiovascular disease. Caution should be exercised when treating subjects whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention.

Prednisone/prednisolone may be associated with fatigue, increased appetite, insomnia, weakness, hyperglycemia, ecchymosis, and symptoms related to gastroesophageal reflux. With long-term glucocorticoid therapy, subjects may develop Cushing's syndrome, characterized by central obesity, thin skin, easy bruising, bone loss, avascular necrosis of the hip, cataract and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise.

The combination of niraparib and AAP was evaluated in the Phase 1b study of subjects with mCRPC (Study 64091742PCR1001). In this study, 27 subjects were included in the Safety Population; 19 subjects in the niraparib 200 mg plus AAP cohort and 8 subjects in the niraparib 300 mg plus AAP cohort.

No dose-limiting toxicities (DLTs) were reported in the niraparib 200 mg plus AAP cohort during Cycle 1 of the study (ie, the 28-day DLT evaluation period). In the niraparib 300 mg plus AAP cohort, 1 DLT of Grade 3 fatigue, possibly related to niraparib and AAP, was reported in a patient treated with niraparib 300 mg plus AAP; the niraparib dose was reduced, and the event did not resolve. Two DLT-like events of Grade 4 neutropenia occurred at Day 29.

All patients (both niraparib 200 mg plus AAP and niraparib 300 mg plus AAP) reported at least 1 or more AEs of any grade. More Grade 3 or 4 events were observed in the niraparib 300 mg plus AAP cohort (88%) than in the niraparib 200 mg plus AAP cohort (58%). The most frequently reported TEAEs were nausea and vomiting in the 200 mg plus AAP cohort and fatigue in the 300 mg plus AAP cohort. The niraparib 300 mg plus AAP cohort also had more SAEs (38%) and TEAEs leading to dose interruption/reduction (25%) than the niraparib 200 mg plus AAP cohort (16% and 16%, respectively). AEs of special interest (AESIs) in this study are hematologic toxicities and hypertension. Thrombocytopenia, anemia, and neutropenia were reported in 6 (31.6%), 3 (15.8%), and 3 (15.8%) patients, respectively, in the niraparib 200 mg plus AAP cohort and 1 (12.5%), 2 (25.0%), and 2 (25.0%) patients, respectively, in the niraparib 300 mg plus AAP cohort. Hypertension of any grade was reported in 5 (26.3%) patients in the niraparib 200 mg plus AAP cohort and 1 (12.5%) patient in the niraparib 300 mg plus AAP cohort. No cardiac or cardiovascular-related deaths were observed in this study.

The PK results showed the absence of a significant interaction between niraparib and AAP. The PK parameters of niraparib when co-administered with AAP were within the target ranges of niraparib monotherapy based on historical data.

The preliminary data observed to date show that the combination of niraparib plus AAP has a safety profile that is similar to the safety profile of each drug alone. Given that subjects in the niraparib 200 mg plus AAP cohort had fewer SAEs, AESIs, and TEAEs leading to dose

interruption/reduction, as well as no DLT or DLT-equivalent Grade 4 toxicities, a dose of niraparib 200 mg was chosen as the RP2D for the combination.

1.3.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

Refer to Section 1.2, for a summary of nonclinical and clinical data for niraparib and Section 1.3.2, for a summary of data on the combination of niraparib and AA administered as single agents. Information regarding the niraparib/AA FDC is in the niraparib/AA fixed-dose combination IB.[25]

1.4. Benefit/Risk Assessment

1.4.1. Combination 1: Niraparib and Cetrelimab

The combination of niraparib with cetrelimab is anticipated to have a positive benefit-risk profile when used for the treatment of patients with metastatic prostate cancer, as proposed for this study. This assessment is based on the following:

- The nonclinical safety profiles for niraparib and cetrelimab appear to be non-overlapping and distinct. Based on available nonclinical data, no additional relevant nonclinical findings are anticipated for the niraparib and cetrelimab combination.
- The PK profiles of niraparib and cetrelimab are distinct, and drug-drug interactions are not expected. Based on their PK profiles and mechanisms of action, the risk of synergistic adverse effects between niraparib and cetrelimab is considered low.
- The safety profiles for niraparib and cetrelimab appear to be non-overlapping based on currently available data, and additional safety risks are not anticipated for niraparib and cetrelimab combination. Adverse events associated with niraparib are primarily hematologic and readily manageable, while those associated with cetrelimab are mainly immune-mediated and are also manageable.
- The proposed niraparib dose was selected based on available data from the ongoing niraparib program. Niraparib has been combined with immune checkpoint inhibitors previously (pembrolizumab, a PD-1 inhibitor/TOPACIO study). In the TOPACIO study, 1 of 6 DLT-eligible subjects was reported with multiple DLTs (Grade 3 anemia, Grade 4 neutropenia, and Grade 4 thrombocytopenia) at a dose of niraparib 200 mg once daily. At a niraparib dose of 300 mg once daily, 1 of 6 subjects was reported with 1 DLT of Grade 4 thrombocytopenia; however, shortly after the evaluable period, a second subject experienced AEs of epistaxis and Grade 4 thrombocytopenia that were considered DLT-equivalent. No significant overlapping toxicities were observed. Niraparib 200 mg once daily in combination with pembrolizumab 200 mg IV every 3 weeks was selected as the RP2D in the study.[32]

  The TOPACIO study has since been amended such that subjects who tolerate niraparib 200 mg once daily for at least 2 cycles have the option to escalate to niraparib 300 mg once daily, if they meet certain hematologic parameters, a strategy that will also be included in the proposed study, 64091742PCR2002. This strategy is supported by a recent safety update (as of August 2017) from the TOPACIO study in which less than 7% of subjects in the dose expansion phase of the study have been reported with Grade ≥3 thrombocytopenia during the first treatment cycle, and in the 2 subjects who were

escalated from niraparib 200 to 300 mg after 2 cycles, no Grade ≥3 events have been reported.[32]

- The proposed doses of cetrelimab were selected based on preliminary data from the ongoing Study 63723283LUC1001, in which safety and antitumor activity was established at both proposed doses. Though more subjects have been treated with the 240 mg once every 2 weeks dosing schedule, the 480 mg once every 4 weeks dose is pharmacologically equivalent to 240 mg every 2 weeks based on preliminary PK data and is preferable for subject convenience. Both dose regimens will be explored in this study.

Studies with the combination of similar PARP inhibitors and immune checkpoint inhibitors, support the combination of niraparib and cetrelimab, which could potentially be a new treatment option for men with mCRPC. The safety profiles for niraparib and cetrelimab appear to be non-overlapping and manageable. The protocol design incorporates appropriate risk mitigation measures, including a safety run-in period, SET monitoring, and targeted safety assessments. Based on the information on the mechanism of action for both agents, completed nonclinical studies, and the available clinical data, the sponsor considers that the assessment of benefit-risk supports the administration of niraparib and cetrelimab combination in patients with mCRPC.

1.4.2. Combination 2: Niraparib and AAP

The combination of niraparib with AAP is anticipated to have a positive benefit-risk profile when used for the treatment of patients with metastatic prostate cancer, as proposed for this study. This assessment is based on the following:

- AAP is an established standard-of-care (SOC) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and since 2015, AAP has been used more commonly than other SOC therapies in patients with first-line mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for androgen deprivation therapy).
- While niraparib is an investigational agent in the metastatic prostate cancer population, it has been approved for the treatment of ovarian cancer and has a safety profile that has been characterized through the conduct of clinical studies (see Section 1.2). Preliminary data from sponsor studies to date suggest that the safety profile of niraparib in patients with metastatic prostate cancer is similar to that described in the Zejula® label.[62] Known toxicities for niraparib include gastrointestinal events, hematological events (ie, thrombocytopenia, neutropenia, anemia), and hypertension; however, these toxicities are manageable with laboratory monitoring and appropriate intervention, such as dose interruptions. The sponsor has also included a targeted monitoring plan and treatment guidelines to ensure appropriate management of these known toxicities.
- The toxicities for AAP are well established and include liver function abnormalities, hypokalemia, and hypertension. These toxicities are manageable with interventions, including proactive laboratory monitoring, dose interruptions, and dose reductions, if needed. Preliminary data from sponsor Study 64091742PCR1001 (see Section 1.3.2) show that niraparib and AAP can be combined safely. No overlap has been noted in the toxicity profiles of niraparib and AAP, with the exception of hypertension, which can be managed medically.
- PK data from Study 64091742PCR1001 also show that exposures for both drugs were comparable to both compounds administered as a single agent.

Given that the anticipated toxicities of both AAP and niraparib are recognizable through medical oversight and laboratory monitoring and are able to be managed medically, and there is a potential for increased efficacy of the combination for patients with incurable metastatic prostate cancer, the sponsor considers that there is a positive benefit/risk profile and strong rationale for evaluating niraparib with AAP for the treatment of patients with metastatic prostate cancer.

1.4.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

The benefit-risk profile for the niraparib/AA FDC tablet is expected to be the same as for niraparib and AA administered as SAs (Section 1.4.2).

The combination of niraparib plus AAP during the PK Assessment Phase in Combination 3 will be administered to subjects with mCRPC, regardless of HRR gene alteration status. If not already known, biomarker status assessment is recommended, and results can be used to guide further treatment decisions during the Extension Phase. If the subject has had a previous result from the sponsor's required assays or a local result from a CLIA-certified or equivalent laboratory, then after the subject grants a release, the data can be reviewed for biomarker status.

As discussed in Section 1.1.3, review of the safety data from Cohort 2 (subjects without HRR gene alterations) randomized to the niraparib and AAP arm of the MAGNITUDE Study showed that 11 subjects (9%) had AEs leading to niraparib interruption or dose reduction within the first 30 days of treatment, and 2 subjects (2%) experienced AEs (glaucoma and increased ALT) requiring niraparib interruption or dose reduction within the first 8 days of treatment. These data from the MAGNITUDE study support the combined daily administration of niraparib and AAP.

In this study, after completion of the PK Assessment Phase and during the Extension Phase, subjects will be allowed to continue niraparib and AAP or AAP alone at the investigator's discretion, informed by biomarker status as well as tolerability for individual subjects. Subjects with HRR gene alterations will be recommended to continue combination treatment with niraparib and AAP. Subjects without HRR gene alterations or those with unknown biomarker status may continue therapy with niraparib and AAP or AAP alone at the investigator's discretion.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

See Attachment 6 for Objectives, Endpoints, and Hypotheses for Combination 3.

2.1. Objectives and Endpoints

Each combination study in this protocol comprises 2 parts; Part 1 will support the dose selection for the niraparib combination therapies, as well as include PK sampling to evaluate for potential drug-drug interactions, and Part 2 (dose expansion) will evaluate the RP2D of each niraparib combination therapy in an expanded number of subjects. For combinations with a previously established RP2D and drug-drug interaction data, Part 1 will not be conducted. The overall objectives and endpoints for the study are provided in Table 1 and Table 2.

See Attachment 6, Section 2.1, for Objectives and Endpoints for Combination 3.

Table 1: Objectives and Endpoints for Part 1	
Objectives	**Endpoints**
Primary	
• To evaluate the tolerability of niraparib combination therapies for the treatment of mCRPC • Determine the RP2D of niraparib combination therapies	• Incidence of specified toxicities (described in Section 3.4)
Secondary	
• To characterize the PK and immunogenicity (if applicable) of niraparib combination therapies	• Plasma concentrations of niraparib and, if performed, its major metabolite (M1), and plasma or serum concentrations of the combination agent • Population PK parameters and derived exposure of niraparib and combination agent • Anti-drug antibodies (if applicable)

mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetics; RP2D=recommended Phase 2 dose

Table 2: Objectives and Endpoints for Part 2	
Objectives	**Endpoints**
Primary	
• To evaluate the antitumor effect of the RP2D of niraparib combination therapies for treatment of mCRPC	**Combination 1** • Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by RECIST 1.1 with no evidence of bone progression according to PCWG3 criteria[50]
	Combination 2 • Composite response rate (RR): defined as 1 of the following by PCWG3:[50] – Objective response (confirmed per RECIST 1.1), or CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later, or – PSA decline of ≥50%, measured twice 3 to 4 weeks apart
• To evaluate the safety of the RP2D of niraparib combination therapies for the treatment of mCRPC	**Combinations 1 and 2** • Incidence and severity of AEs
Secondary	
• To evaluate other response outcomes of niraparib combination therapies for the treatment of mCRPC	**Combinations 1 and 2** • CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at

Table 2: Objectives and Endpoints for Part 2	
Objectives	**Endpoints**
	baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later **Combination 1 only** • Composite response rate (RR): defined as 1 of the following by PCWG3:[50] – Objective response (confirmed per RECIST 1.1), or – CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later, or – PSA decline of ≥50%, measured twice 3 to 4 weeks apart. **Combination 2 only** • Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by RECIST 1.1 with no evidence of bone progression according to PCWG3 criteria[50]
• To evaluate duration of response	**Combinations 1 and 2** • 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 • OS: time from enrollment to death from any cause
• To characterize the PK and immunogenicity (if applicable) of niraparib combination therapies through sparse sampling	**Combination 1 only** • Plasma concentrations of niraparib and, if performed, its major metabolite (M1) when dosed with combination agent • Population PK parameters and derived exposure of niraparib and combination agent • Anti-drug antibodies (if applicable)

Table 2: Objectives and Endpoints for Part 2	
Objectives	**Endpoints**
Exploratory	
• To evaluate MOAs for niraparib combination therapies, as well as potential biomarkers predictive of response and resistance	**Combination 1 only** • Assessment of biomarkers related to MOAs or response/resistance for niraparib, other anticancer agent, or the combination at baseline, on-treatment, and at progression
• To explore potential relationships between the PK of niraparib combination therapies, and any associated clinical activity, pharmacodynamic markers, or safety signals	**Combination 1 only** • Changes in levels of pharmacodynamic markers (eg, PSA, CTCs)

AE=adverse event; CR=complete response; CTC=circulating tumor cell; mCRPC=metastatic castration-resistant prostate cancer; MOA=mechanism of action; ORR=objective response rate; OS=overall survival; PCWG3=Prostate Cancer Working Group 3; PR=partial response; PK=pharmacokinetics; PSA=prostate-specific antigen; RECIST= Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; RR=response rate

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

2.2. Hypotheses

Part 1 (Safety Run-in): An RP2D of niraparib when combined with other anticancer agents can be identified.

Part 2 (Dose Expansion): Niraparib administered in combination with other anticancer agents at the selected RP2D is safe and has antitumor activity.

2.2.1. Combination 1: Niraparib and Cetrelimab

The hypotheses for this combination are:

- That cetrelimab inhibition of PD-1 complements the antitumor activity of the PARP inhibitor, niraparib, for effective and safe treatment of subjects with mCRPC with DRD or CDK12 pathogenic alterations.
- The combination of niraparib and cetrelimab is safe and has antitumor activity in subjects with mCRPC with DRD or CDK12 pathogenic alterations.

2.2.2. Combination 2: Niraparib and AAP

The hypothesis for this combination is:

- Androgen receptor (AR) inhibition enhances the antitumor activity of PARP inhibition for the effective and safe treatment of subjects with mCRPC and DRD. A response rate of 62% is expected for subjects with biallelic DRD, and 57% for subjects with monoallelic DRD.

2.2.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

See Attachment 6, Section 2.2, for Hypothesis for Combination 3.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 1b-2, multicenter, open-label study to select the RP2D of niraparib in combination with other anticancer agents, followed by dose expansion that will enroll adult subjects with mCRPC who are either BM+ or BM- for DRD or BM+ for CDK12 pathogenic alterations (see Section 9.5, for description of biomarker-positivity criteria). Details regarding combination-specific study design considerations are provided in the corresponding subsections below.

The primary objectives of the study are to establish the RP2D of niraparib with various combination agents (Part 1) and to evaluate the antitumor activity and safety of niraparib with various combination agents (Part 2). Other objectives may include evaluating the PK of niraparib and combination agents and investigating potential biomarkers that establish the pharmacodynamic effect of each combination.

Each combination study will have 5 phases: a Prescreening Phase, a Screening Phase, a Treatment Phase, a Follow-up Phase (see Section 9.1, and the Time and Events Schedules for details), and a Long-term Extension Phase (see Attachment for details). Treatment cycles will be 28 days. Subjects will begin receiving treatment on Cycle 1 Day 1, as described in Section 6. All subjects will continue to receive the study drugs until disease progression, unacceptable toxicity, death, or the sponsor terminates the study (see Section 10). Subjects will be monitored for safety during the Prescreening, Screening, and Treatment Phases, and for up to 100 days after the last dose of study drugs for Combination 1 and 30 days after the last dose of study drugs for Combination 2.

The end of the overall study (study completion) is defined as the last study assessment for the last subject on study. However, each combination will also have a study completion date, defined as the last study assessment for the last subject on each combination. Data for each combination will be reported in a separate clinical study report (CSR). The sponsor may also establish an interim data cutoff date for each CSR analysis at an earlier timepoint than the study completion date. The data cutoff will be communicated to the sites. Subjects who continue to receive study drugs after the data cutoff will continue to be monitored and data will be collected on study drug administration, AEs, SAEs, laboratory abnormalities indicative of an AE, and concomitant medications used to treat these events.

In the event of early study completion or study termination by the sponsor, (whether or not the study endpoints are met), the sponsor will continue to provide study treatments until unequivocal disease progression, unacceptable toxicity, or an alternate method is in place to avoid treatment interruption.

3.1.1. Combination 1: Niraparib and Cetrelimab

This combination study will enroll adult subjects with mCRPC who are either BM+ (Cohort 1A) or BM- (Cohort 1B) for DRD or BM+ for CDK12 pathogenic alterations based on the sponsor's blood or tissue assay. A schematic for this combination is provided in Figure 1.

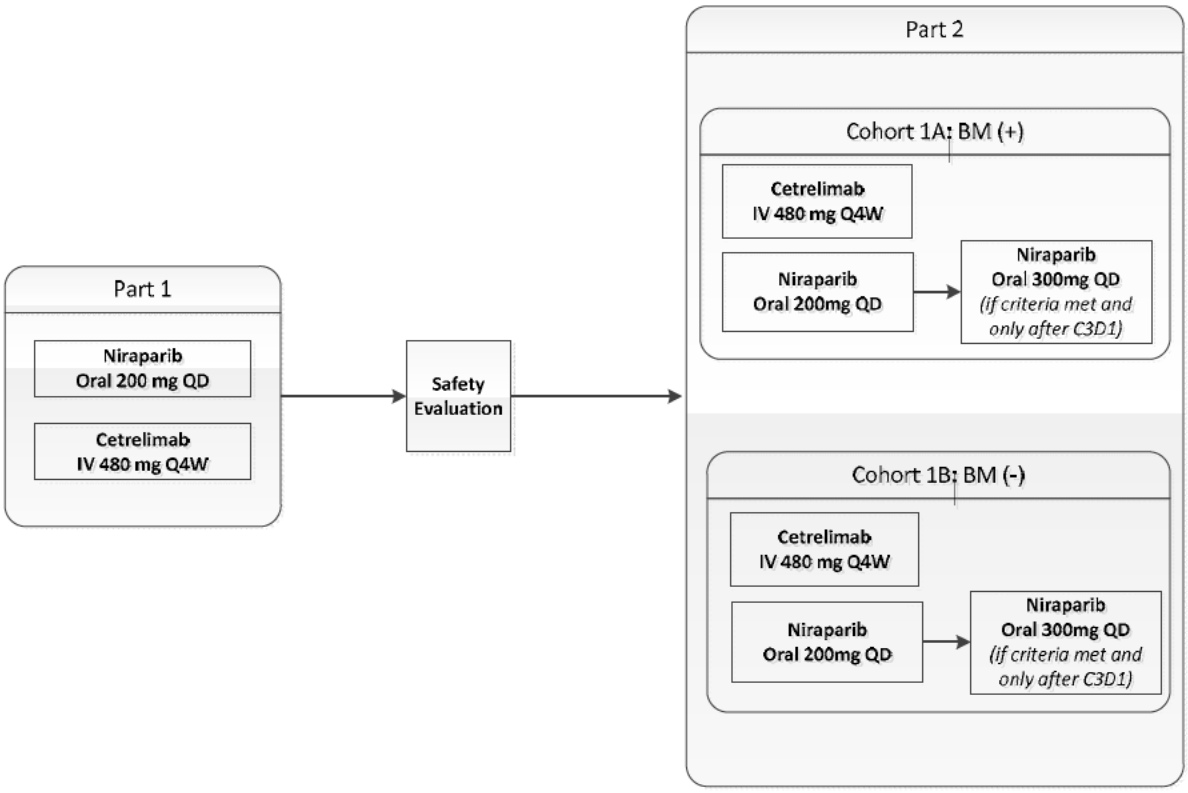
For Part 1 at least 6 evaluable subjects will be treated with niraparib 200 mg orally once daily in combination with cetrelimab 480 mg IV once every 4 weeks.

Evaluable subjects for Part 1 are defined as those who have an event as defined by the safety evaluation criteria (see Section 3.4) in Cycle 1, or complete at least 1 cycle of treatment and receive at least 75% of the planned study drugs (ie, 75% niraparib capsules and 75% of cetrelimab infusion/s). Non-evaluable subjects will be replaced. After at least 6 evaluable subjects have completed the safety assessment period, a safety evaluation team (SET; see Section 3.5) will assess the available data to determine the safety of the combination and make a decision to proceed with Part 2 of the study (see Section 3.4). The sponsor may choose to enroll subjects to additional dose regimens (ie, at least 6 additional evaluable subjects) with cetrelimab and a modified dose of niraparib (ie, 100 mg or 300 mg), depending on the available data obtained from the niraparib 200 mg cohorts. The sponsor, in discussion with the SET, will decide which dose regimen will be used for Part 2 of the study. After the safety evaluation period, the evaluable subjects will continue in the study (Part 2) and will be evaluated in the final analysis based on their biomarker status (ie, BM+ or BM-). If a subject was enrolled into the cetrelimab 240 mg every 2-week regimen under a prior version of the protocol, the subject should be transitioned to cetrelimab 480 mg every 4 weeks once the protocol amendment and revised informed consent form (ICF) are approved at the site, as required by local regulations.

Once an RP2D has been established for the combination in Part 1, approximately 30 subjects will be enrolled per cohort for Part 2. Note that a futility analysis was performed for Cohort 1B after approximately 10 subjects have been enrolled and evaluated in Part 2 (see Section 11.10). All subjects will be assigned to a cohort based on their biomarker status for DRD or CDK12 (ie, Cohort 1A BM+ or Cohort 1B BM-), which will be determined during the Prescreening Phase using the sponsor blood or tissue assay. The total number of subjects to be enrolled in the study is described in Section 11.2.

If a dose of niraparib 200 mg once daily is selected for the RP2D, then all subjects may receive an escalated dose of niraparib 300 mg once daily on or after Cycle 3 Day 1, if they meet the following criteria: platelets $\geq 100 \times 10^9$/L, hemoglobin ≥9.0 g/dL, and neutrophils $\geq 1.5 \times 10^9$/L for all laboratory tests performed during the first 2 cycles after discussion with the medical monitor.

Figure 1: Schematic for Combination 1



Q4W once every 4 weeks
Note: For Part 2, the RP2D of niraparib is assumed to be 200 mg once daily; however, the SET will determine if an additional cohort evaluating either 100 mg or 300 mg niraparib is necessary, based on the data from dose regimens 1 and 2. The option for escalation to niraparib 300 mg on or after Cycle 3 Day 1 will only occur if the RP2D for niraparib is 200 mg.

Note: The Long term Extension Phase is not included in the schematic.

Study Continuation Under Amendment 6 for Combination 1

Based on the results of a pre-planned futility analysis, Cohort 1B was closed to enrollment on 30 May 2019. Based on Data Review Committee (DRC) review and recommendation from a meeting on 8 July 2020, Cohort 1A is closed to enrollment under Amendment 6 (see Section 11.10).

Subjects already enrolled in Combination 1 (Cohort A or B) can continue to receive study medication by following the procedures outlined in Attachment 5. The subject is considered to have completed the study after discontinuing treatment for any reason and having had a safety assessment at the End-of-treatment Visit or the subject is lost to follow-up.

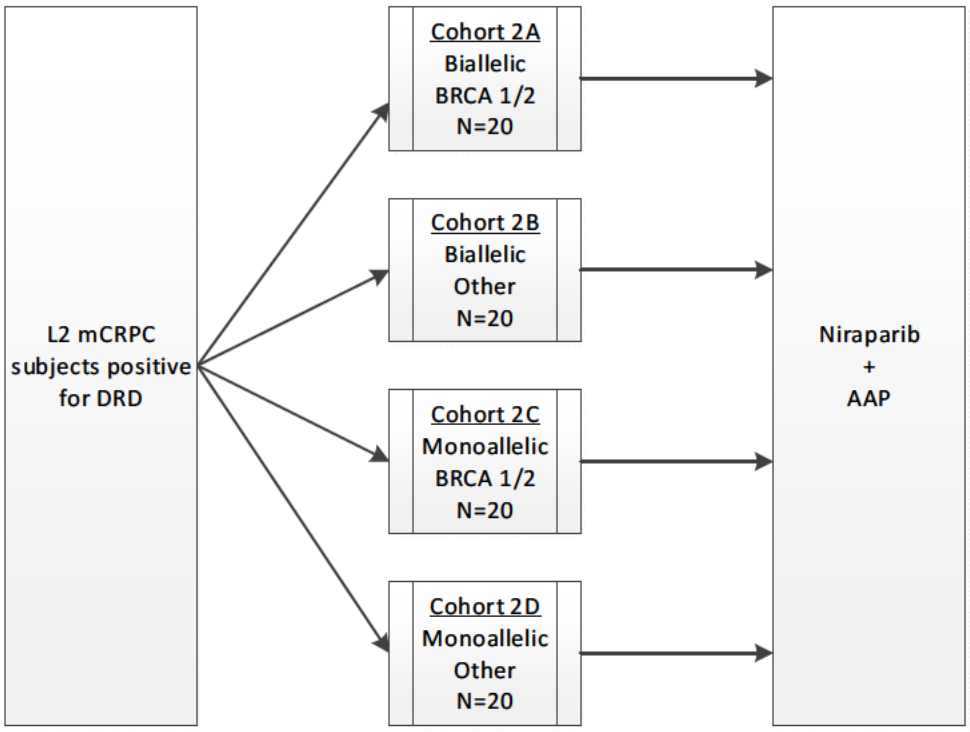
3.1.2. Combination 2: Niraparib and AAP

The RP2D for niraparib plus AAP was established in the sponsor Study 64091742PCR1001 (see Section 1.3.2). Therefore, Part 1 was not conducted in this study for Combination 2.

Combination 2 will explore the safety and efficacy of niraparib plus AAP in mCRPC patients with DRD as determined during the Prescreening Phase using a blood or tissue assay (see Section 9.5). In Part 2, subjects will be enrolled into 4 cohorts (BRCA biallelic loss [2A], other DRD biallelic

loss [2B], BRCA monoallelic loss [2C], and other DRD monoallelic loss [2D]), with approximately 20 subjects in each cohort. A schematic for this combination is provided in Figure 2.

Figure 2: Schematic for Combination 2



Note: The Long term Extension Phase is not included in the schematic.

Study Continuation Under Amendment 4 for Combination 2

Under Amendment 4, Combination 2 has been closed to enrollment. Subjects already enrolled in Combination 2 can continue to receive study medication by following the procedures outlined in Attachment 5. The subject is considered to have completed the study after discontinuing treatment for any reason and having had a safety assessment at the End-of-treatment Visit or the subject is lost to follow-up.

3.1.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

See Attachment 6 for an Overview of Study Design for Combination 3.

3.1.4. Long-term Extension Phase for any Combination Subgroup

The Long-term Extension Phase for the specified combination will start once the Amendment 7 has been approved at the site and after the notification by the sponsor (Attachment).

3.2. Dose Selection Rationale

For niraparib, the TESARO Phase 1 study, PN001, demonstrated antitumor activity at doses ranging from 80 to 400 mg, as illustrated by ≥50% inhibition of PARP activity in circulating peripheral blood mononuclear cells of subjects at steady-state (ie, by Cycle 1 Day 5).[47] The

FDA-approved single-agent dose for treatment of ovarian cancer is 300 mg once daily, based on the NOVA study that evaluated single agent niraparib as maintenance therapy in subjects with platinum-sensitive recurrent ovarian cancer.[36] However, dose reductions and interruptions due to hematologic toxicities have been common at that dose.

3.2.1. Combination 1: Niraparib and Cetrelimab

The proposed starting dose of niraparib for this combination (ie, 200 mg) is based on the RP2D from the Phase 1 portion of the TOPACIO study, which is a combination study of niraparib plus pembrolizumab for treatment of triple-negative breast cancer or platinum-resistant ovarian cancer. Subjects were enrolled at 2 dose levels: Dose Level 1 (niraparib 200 mg once daily and pembrolizumab 200 mg IV every 3 weeks) or Dose Level 2 (niraparib 300 mg once daily and pembrolizumab 200 mg IV every 3 weeks). Out of 14 subjects, 12 were eligible for DLT evaluation. At Dose Level 1, 1 of 6 DLT-eligible subjects was reported with multiple DLTs, including Grade 3 anemia, Grade 4 neutropenia, and Grade 4 thrombocytopenia. At Dose Level 2, 1 of 6 DLT-eligible subjects was reported with 1 DLT of Grade 4 thrombocytopenia. An additional subject was reported with an AE that was deemed to be DLT-equivalent; the subject had epistaxis and Grade 4 thrombocytopenia soon after the DLT period. No significant overlapping toxicities were noted and the RP2D for the TOPACIO study was established as niraparib 200 mg once daily plus pembrolizumab 200 mg IV every 3 weeks.

However, niraparib 300 mg once daily is the FDA-approved dose for monotherapy treatment (for ovarian cancer) and novel strategies are being designed to improve subject selection for this dose while minimizing toxicity. The TOPACIO study has been amended such that subjects who tolerate niraparib 200 mg once daily for at least 2 cycles have the option to escalate to niraparib 300 mg once daily, if they meet certain hematologic parameters (see Section 3.1.1). This staggered escalation strategy prevents needless toxicity in those subjects who are unable to tolerate the higher dose of niraparib, while allowing those who can tolerate the higher dose to potentially maximize antitumor activity. This strategy is supported by a recent safety update from the TOPACIO study, which reported that less than 7% of Phase 2 subjects have been reported with Grade ≥3 thrombocytopenia during the first treatment cycle and that the 2 subjects who have been escalated from niraparib 200 mg to 300 mg after 2 cycles have had no Grade ≥3 events to date.

For cetrelimab, the 480 mg once every 4 weeks dosing schedule was selected as it is an RP2D in the cetrelimab single agent study (Study 63723283LUC1001) and is preferable to the 240 mg once every 2 weeks dosing for subject convenience.[22]

3.2.2. Combination 2: Niraparib and AAP

The RP2D of niraparib in combination with AAP is 200 mg based on Study 64091742PCR1001 (See Section 1.3.2). The data from that study showed that the combination of niraparib plus AAP has a safety profile that is similar to the safety profile of each drug alone.

3.2.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

See Section 3.2.2.

3.3. Biomarker Rationale

Subjects who are BM+ or BM- for DRD or BM+ for CDK12 may demonstrate different responses to treatment with niraparib combination therapy. Note that cohort eligibility is different for each combination, see Section 9.5, and Table 9 for details. In addition, analyzing the changes in biomarkers that correspond with each subjects' response may help to understand the MOA of that response. For this reason, there are 2 parts to the biomarker plan for this protocol, as follows:

- DRD and CDK12: Subjects in Combinations 1 and 2 will be prospectively assessed in the prescreening phase to determine their biomarker status: DRD and CDK12 for Combination 1 and DRD for Combination 2 based on the criteria described in Section 9.5.
- Exploratory biomarker collection for MOA determination for Combination 1: Biomarker samples will be collected at the timepoints outlined in Time and Events Schedule 1 to analyze the biological activity, MOA, and resistance mechanisms of the niraparib combination therapy before, during, and after treatment.

3.3.1. Combination 1: Niraparib and Cetrelimab

Published results suggest that the expression of PD-L1 in some tumors correlates with response to anti-PD-L1 therapy.[20,54] In addition, mCRPC tumors with BRCA1 and/or BRCA2 mutations had higher mutational burden compared to those without DRD.[41] This increased mutational burden may create neoantigens and correlate with response to anti-PD-L1 therapy. Therefore, PD-L1 expression, DRD and CDK12 will be retrospectively evaluated in tumor biopsies. To understand the MOA of niraparib and cetrelimab in combination, tumor biopsies will also be retrospectively evaluated for other immune- or prostate cancer-related biomarkers, such as tumor mutational burden, and T-cell clonal change. Circulating immune- and tumor-related biomarkers will also be evaluated as potential pharmacodynamic and response biomarkers.

Additional details of the biomarker evaluation plan are provided in Section 9.5. Full details of the exploratory biomarker analyses will be included in a biomarker Statistical Analysis Plan for this combination.

3.3.2. Combination 2: Niraparib and AAP

As noted in Section 1.1.2, the combination of the PARP inhibitor, niraparib, and the AR-targeted therapy, AAP may be a safe and effective treatment for patients with metastatic prostate cancer who have DRD. However, it is not known whether the type of mutation and gene may determine response to the combination. mCRPC tumors with BRCA1 and/or BRCA2 mutations have been found to have higher mutational burden compared to those without DRD, suggesting that these tumors have different biologic behavior.[41] Preclinical work has found dual roles for PARP in supporting AR activity in which PARP-1 is a potent modulator of both AR function and response to DNA damage.[51] Therefore, this combination may be complementary because AR-controlled DRD genes may affect efficient assembly of the DRD complex. To further evaluate this question, this study will enroll DRD patients prospectively into 4 cohorts (BRCA biallelic loss [2A], other DRD biallelic loss [2B], BRCA monoallelic loss [2C], and other DRD monoallelic loss [2D]) in order to investigate differences in efficacy to the combination of niraparib and AAP.

3.3.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

For Combination 3, biomarker status is not required to determine study eligibility. If not already known, biomarker status assessment is recommended, and results can be used to guide further treatment decisions during the Extension Phase (see Attachment 6).

3.4. Safety Evaluation Criteria for Part 1

For each combination, the safety evaluation period is defined as the first 28 days of treatment (ie, Cycle 1) for the subjects in Part 1. If a subject receives less than 75% of each assigned dose during Cycle 1 due to reasons other than for a specified toxicity criterion as described in this section (eg, disease progression, missed appointments, non-compliance, subject withdrawal), then the individual is not evaluable and may be replaced with a new subject.

A SET will meet after at least 6 evaluable subjects have completed the safety assessment period. The SET will determine if a lower or higher dose cohort should be evaluated prior to proceeding with the dose expansion part of the study (ie, 100 mg or 300 mg of niraparib). If more than 33% of subjects (eg, more than 2 out of 6 subjects) in Part 1 have a specified toxicity (see criteria below), then a new dose cohort will be opened with niraparib 100 mg once daily (ie, at least 6 new evaluable subjects will be enrolled). If the SET determines that a higher dose of niraparib should be explored (ie, niraparib 300 mg once daily), then a new dose cohort will be added with an additional 6 evaluable subjects. All available safety data from non-evaluable subjects will also be taken into consideration by the SET. The number of evaluable subjects per cohort enrolled in Part 1 may be expanded up to 9 at the discretion of the sponsor.

Note that after Cycle 1, subjects may continue to receive additional cycles of their originally assigned dose of niraparib and cetrelimab while the study continues to enroll and other subjects complete their evaluation period. Enrollment into Part 1 dose regimens will continue unless >2 subjects are reported with a specified toxicity, at which time new subject enrollment will stop in that dose regimen until after the SET convenes and makes recommendations regarding conduct of the study.

Toxicities will be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 or later. Only toxicities that occur during the safety evaluation period will be used for the purpose of defining specified toxicities and for dose reduction decisions, but toxicities that occur during the entire treatment period will be recorded and considered in decisions regarding dose expansion and escalation. Cases may be discussed with the SET, if needed, to determine if toxicity meets the criteria.

The safety evaluation criteria are as follows:

- Any Grade ≥3 non-hematological toxicity, with the following exceptions:

  Anorexia, fever, or constipation

  Fatigue that improves to Grade ≤2 in ≤7 days

  Nausea lasting for ≤7 days responding to best supportive care

Vomiting and diarrhea that resolves in ≤3 days with best supportive care

Laboratory abnormalities that do not require hospitalization and are not deemed to be clinically significant by the investigator

Tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) that improves to Grade ≤2 in ≤7 days

Elevation in AST or ALT for ≤7 days

Grade 3 hypertension that is controllable by medical therapy

- Any treatment-related Grade 4 thrombocytopenia or Grade ≥3 thrombocytopenia requiring platelet transfusion.
- Any treatment-related Grade 4 neutropenia ≥7 days, or Grade 3 or 4 neutropenia associated with infection or fever >38.5 degrees Celsius.
- Any treatment-related SAE or subjectively intolerable toxicity judged by the SET as related to study drugs.

Additional safety evaluation criteria for combination agents with a unique safety profile will be added in subsections below, as appropriate.

3.5. Safety Evaluation Team (Combinations with Part 1)

A SET will be established by the sponsor for each combination. The SET consists of study investigators, the sponsor compound clinical leaders, the sponsor medical monitor, the sponsor medical safety officer, and the sponsor clinical pharmacologist; the sponsor statistician will be consulted, as needed. The SET convenes as necessary for review of safety-related issues and must meet after at least 6 evaluable subjects complete the safety assessment period for a given combination. Any SET member may request a SET meeting, which should be convened within 3 working days. The SET reviews PK information and all safety data, including SAE, and all Grade ≥3 AEs, including toxicity appearing after the safety evaluation period.

Decisions on dose reduction/modification, change in PK sampling times, and change in study drug dosing and schedule in Part 1 will be performed in collaboration with the SET, and will be based on available data and the following factors:

- AE profile (type, severity, onset, and duration)
- PK (C_{max}/AUC)
- Antitumor activity (clinical, biochemical, and radiographic data)

While the SET is reviewing the safety data, remaining subjects in Part 1 who have not been reported with a specified toxicity (as described in Section 3.4) may continue to receive additional cycles of their assigned dose of niraparib and combination agent, after consultation with the sponsor. The established SET will monitor all available treatment-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of subjects enrolled in this study. The SET will also be responsible for making a formal determination of whether the study will proceed to Part 2.

Decisions made by the SET will be documented and communicated to study investigators before administration of study drugs to any subsequent subject. The Institutional Review Board (IRB)/independent ethics committee (IEC) for each combination will be notified before implementation of any SET decision, if required. Documented decisions should be retained in the study master file and in study-site files. Decisions with the potential to affect subject safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and regulatory authorities as appropriate.

Note: a DRC will be established to monitor safety, study-related data, and study conduct for Part 2 of each combination (see Section 11.9).

The SET does not apply for Combination 3.

4. SUBJECT POPULATION

See Attachment 6 for a description of the Subject Population, Inclusion and Exclusion Criteria for Combination 3.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers for study eligibility criteria are not allowed. Screening for eligible subjects will be performed within 28 days before administration of the study drugs, unless otherwise specified. Combination-specific eligibility criteria are provided in separate subsections, as appropriate.

4.1. Prescreening Eligibility Criteria

The following criteria must be met:

1. Criterion modified per Amendment 4.

   1.1 Signed prescreening informed consent form.

2. Criterion modified per Amendment 4.

   2.1 Criterion modified per Amendment 5.

   2.2 Willing to provide a blood and tissue sample for analysis of DRD and CDK12 pathogenic alterations. Note: If the subject has a previous local test result (from a Clinical Laboratory Improvement Amendments [CLIA]-certified or equivalent laboratory), the data can be reviewed by the sponsor for determination of DRD and CDK12 pathogenic alteration.

3. Criterion moved to Section 4.1.1, per Amendment 3.

4. Criterion deleted per Amendment 3.

4.1.1. Combination 1: Niraparib and Cetrelimab

In addition to the criteria in 4.1, each potential subject for Combination 1 must satisfy the following criteria:

1. At least 1, but no more than 2, lines of novel AR-targeted therapy (ie, abiraterone acetate with prednisone, enzalutamide) for mCRPC. Subjects must have had at least 4 weeks of AR-targeted therapy.

4.1.2. Combination 2: Niraparib and AAP

In addition to the criteria in 4.1, each potential subject for Combination 2 must satisfy the following criteria:

1. Must have progressed on 1 prior line of novel AR-targeted therapy (ie, abiraterone acetate with prednisone, enzalutamide) for mCRPC. Prior treatment with taxane-based therapy and AR-targeted therapy outside of the mCRPC setting are allowed.

4.2. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Criterion modified per Amendment 2.
   1.1 18 years of age or older.
2. Willing to undergo all protocol-specified biopsies.
3. Diagnosis of prostate adenocarcinoma as confirmed by the investigator.
4. Criterion moved to Section 4.2.1, per Amendment 3.
5. Criterion moved to Section 4.2.1, per Amendment 3.
6. Criterion moved to Section 4.2.1, per Amendment 3.
7. Must have castrate levels of testosterone ≤50 ng/dL on a gonadotropin releasing hormone analogue (GnRHa), or history of bilateral orchiectomy at study entry.
8. Progression of metastatic prostate cancer 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).[50] The PSA level at the screening visit should be ≥2 µg/L (2 ng/mL).
   b. Radiographic progression by bone scan per PCWG3 or by soft tissue per RECIST 1.1.[9,50]
9. Must be willing to continue GnRHa during the study if not surgically castrate.
10. Eastern Cooperative Oncology Group Performance Score (ECOG PS) Grade of 0 or 1 (see Attachment 2).

11. Criterion modified per Amendment 3.

    11.1 Subjects who received prior therapy with an anti-androgen (eg, bicalutamide, flutamide, nilutamide, enzalutamide, apalutamide) must have at least a 4-week wash-out prior to enrollment.

12. Criterion modified per Amendment 6.

    12.1 While on study medication and for 3 months (Combination 2) or 5 months (Combination 1) following the last dose of study medication, a male subject must agree to use an adequate contraception method as deemed appropriate by the investigator and as specified in Section 4.4, Lifestyle Considerations.

13. Criterion modified per Amendment 2.

    13.1 Clinical laboratory values at Screening:

    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, independent of growth factors for 30 days
    b. Hemoglobin ≥9.0 g/dL, independent of growth factors or transfusions for 30 days
    c. Platelet count $\geq 100 \times 10^9$/L, independent of growth factors or transfusions for 30 days
    d. Serum albumin ≥3.0 g/dL
    e. Creatinine clearance ≥30 mL/min/1.73 m^2 either calculated or directly measured via 24-hour urine collection.
    f. 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 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 as determined by the medical monitor)
    g. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x ULN
    h. Fasting glucose ≤250 mg/dL

14. A male subject must agree not to donate sperm while on study treatment and for 3 months (Combination 2) or 5 months (Combination 1) following the last dose of study medication.

4.2.1. Combination 1: Niraparib and Cetrelimab

In addition to the criteria in Section 4.2, each potential subject for Combination 1 must satisfy the following criteria:

1. Criterion modified per Amendment 4.

   1.1 Criterion modified per Amendment 5.

   1.2 Must have determination of biomarker positive for DRD (biallelic) or CDK12 pathogenic alterations by the sponsor's blood or tissue assay, or a previous local test result (from a CLIA-certified or equivalent laboratory) and reviewed by the sponsor to confirm eligibility. For Part 1 of the study, subjects can be dosed prior to assay results becoming available. Results are required prior to dosing for Part 2.

2. Subjects must have measurable disease as defined by RECIST 1.1[9] (soft tissue lesion of ≥10mm in the long axis or extrapelvic lymph node of ≥15mm in the short axis).
3. Must have previously received at least 1, but no more than 2, lines of novel AR-targeted therapy (ie, abiraterone acetate with prednisone, enzalutamide) for mCRPC. Subjects must have had at least 4 weeks of AR-targeted therapy.

4.2.2. Combination 2: Niraparib and AAP

In addition to the criteria in Section 4.2, each potential subject for Combination 2 must satisfy the following criteria:

1. Must be biomarker positive for DRD by either the sponsor's blood or tissue assay.
2. Must have progressed on 1 prior line of novel AR-targeted therapy (ie, abiraterone acetate with prednisone, enzalutamide) for mCRPC. Prior treatment with taxane-based therapy and AR-targeted therapy outside of the mCRPC setting are allowed.

4.3. Exclusion Criteria

Combination-specific exclusion criteria are provided in the appropriate subsections below. Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Prior treatment with a PARP inhibitor.
2. History or current diagnosis of MDS/AML.
3. Criterion modified per Amendment 5.

   Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

   a. non-muscle invasive bladder cancer.
   b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
   c. Breast cancer:
      - adequately treated lobular carcinoma in situ or ductal carcinoma in situ,
      - or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
   d. Malignancy that is considered cured with minimal risk of recurrence.
4. Active infection requiring systemic therapy.
5. Allergies, hypersensitivity, or intolerance to niraparib or the corresponding excipients (refer to the Investigator's Brochures).[24]

6. Human immunodeficiency virus (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 11.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 cells/mm^3 at screening.
    e. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening.
7. Active hepatitis B virus (eg, hepatitis B surface antigen reactive) or active hepatitis C virus (HCV) (eg, HCV ribonucleic acid [RNA] [qualitative] is detected).
8. If a subject has undergone major surgery, they must have recovered adequately from the toxicities or complications from the intervention prior to starting therapy.
9. Criterion deleted per Amendment 2.
10. Any of the following ≤30 days prior to planned Cycle 1 Day 1:
    a. A transfusion (platelets or red blood cells).
    b. Hematopoietic growth factors.
    c. An investigational agent for prostate cancer.
    d. Major surgery (sponsor's medical monitor should be consulted regarding what constitutes major surgery).
    e. Radiation therapy.
11. Symptomatic brain metastasis from prostate cancer.
12. Criterion modified per Amendment 3.

    12.1 Symptomatic congestive heart failure (New York Heart Association Class III or IV heart disease), unstable angina pectoris, cardiac arrhythmia, or uncontrolled hypertension defined as systolic blood pressure [BP] >160 mmHg or diastolic BP >100 mmHg). Note that subjects with a history of hypertension are allowed, if BP is controlled to within these limits by anti-hypertensive treatment.
13. Any condition for which, in the opinion of the investigator or medical monitor, 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.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that the individual no longer meets all eligibility criteria, then the subject should be excluded from

participation in the study. Section 9.1.3, Screening Phase, describes options for rescreening. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3.1. Combination 1: Niraparib and Cetrelimab

In addition to the exclusion criteria in Section 4.3, any potential subject that meets the following criteria will be excluded from participation in Combination 1:

1. Criterion deleted per Amendment 2.
2. Criterion modified per Amendment 2.

   2.1 Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 antibody (including any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
3. Subjects with a history of allergy to protein-based therapies or any significant drug allergy (ie, anaphylaxis, heptatotoxicity, or immune-mediated thrombocytopenia or anemia).
4. History of (non-infectious) pneumonitis that required corticosteroids or current pneumonitis.
5. Allergies, hypersensitivity, or intolerance to cetrelimab or the corresponding excipients (refer to the Investigator's Brochure).[22,]
6. Immunodeficiency or receiving systemic corticosteroid therapy or immunosuppressive therapy (eg, cyclosporine) within 7 days prior to treatment allocation. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
7. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
8. Received a live vaccine within 30 days of the first dose of study drugs.
9. History of organ transplant, including allogeneic stem cell transplantation.

4.3.2. Combination 2: Niraparib and AAP

In addition to the exclusion criteria in Section 4.3, any potential subject that meets the following criteria will be excluded from participation in Combination 2:

1. Allergies, hypersensitivity, or intolerance to abiraterone acetate or prednisone or the corresponding excipients (refer to the Investigator's Brochure).
2. Current evidence of any of the following:

   a. Any medical condition that would make prednisone use contraindicated.

b. Any chronic medical condition requiring a higher dose of corticosteroid than 10 mg prednisone (or equivalent) once daily

4.4. Lifestyle Considerations

Potential subjects must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

Must agree to always use a condom during sexual intercourse (even in case of prior vasectomy or in case of intercourse with an already pregnant woman) or to remain abstinent during the study and for 3 months (Combination 2) or 5 months (Combination 1) after the last study treatment administration (Section 10.2, Discontinuation of Study Treatment).

If the subject is engaged in sexual activity with a woman of childbearing potential, then a condom should be used along with another highly effective contraceptive method. Highly effective methods of contraception (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

combined hormonal (estrogen + progesterone or progesterone only) contraception associated with inhibition of ovulation: oral, injectable or implantable;

placement of an intrauterine device (IUD) or intrauterine hormone releasing system (IUS);

bilateral tubal occlusion;

vasectomy;

sexual abstinence; please note that sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

A highly effective contraceptive method should be used for the duration of the study and for 3 months (Combination 2) or 5 months (Combination 1) after the last study medication administration.

5. TREATMENT ALLOCATION AND BLINDING

See Attachment 6 for Treatment Allocation information for Combination 3.

This is an open-label study; therefore, no blinding or randomization procedures will be performed. Subject information will be entered by the site into the Interactive Web Response System (IWRS) during prescreening and each subject will be assigned a subject identification number. A blood sample will be collected and sent for testing for biomarker status using the sponsor's assay. (Tissue may also be used to determine eligibility as described in Section 9.5). The medical monitor or designee will review selected clinical information and for Part 2 patients, results of biomarker testing in order to assign the subject to the appropriate cohort.

6. DOSAGE AND ADMINISTRATION

See Attachment 6 and Section 6.1.3, below for Dosage and Administration information for Combination 3.

6.1. Study Drug Administration

All dosing information must be recorded in the electronic case report form (eCRF). Supply of study drugs will be managed with a centralized IWRS.

Niraparib will be provided as 100 mg capsules for once daily oral administration. Subjects should take their daily dose of niraparib around the same time every day with or without food. The capsules must be swallowed whole. If a subject forgets to take their dose of niraparib at the regular time, the dose may be taken within 12 hours, otherwise the dose should be omitted. Study-site personnel will use the information in the pharmacy manual to instruct subjects on how to store niraparib for at-home use as indicated for this protocol. For all site visits days and PK or immunogenicity sampling days (as applicable to each combination), the subject must not take niraparib at home in the morning; both study drugs should be administered at the investigational site.

Although not considered study medication, subjects who have not undergone surgical castration must continue to receive regularly prescribed GnRHa. Sites should 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.

6.1.1. Combination 1: Niraparib and Cetrelimab

The treatments to be used for this combination are detailed in Table 3.

Table 3: Study Treatments for Combination 1

Drug	Dose	Dose Frequency	Route of Administration	Regimen
Niraparib	200 mg[a]	Once daily	Oral	2 x 100 mg capsules
Cetrelimab[b]	480 mg	Every 4 weeks	IV infusion	Day 1 of each cycle

IV=intravenous

a This is the starting dose of niraparib. Based on data obtained in Part 1, the dose of niraparib may be reduced to 100 mg once daily, or increased to 300 mg once daily.

b On days that both study drugs are administered, niraparib will be taken at the study site within 0.5 hours before the start of infusion of cetrelimab.

The infusion rate of cetrelimab should allow for the diluted drug product and flush to be infused into the subject over 60 (±10) minutes for the initial dose. In the absence of IRRs or other safety concerns, the infusion rate for subsequent infusions administering ≤100 mL IV bags of diluted drug product may be increased to allow for diluted drug product to be infused into the subject over 30 (±10) minutes. Subjects should be carefully observed during cetrelimab infusions. Trained study staff at the clinic should be prepared to intervene in case of an IRR. Resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered if multiple subjects will be dosed at the same

time. If an IRR develops, then the infusion should be temporarily interrupted or slowed down and the guidelines in Section 6.2.1.2.2, should be followed to manage the IRR.

For the first infusion, vital signs should be monitored before the start of the infusion, every 15 to 20 minutes during the infusion, at the end of infusion, and 2 hours (±15 min) after the end of infusion. After the completion of the first infusion the subject may be discharged if considered clinically stable and all other study procedures have been completed. During subsequent infusions of cetrelimab, vital signs should be monitored predose, once during infusion, and at the end of infusion. cetrelimab infusions will be prepared as described in the Investigational Product Preparation Instructions.

6.1.2. Combination 2: Niraparib and AAP

All subjects will receive AAP from a central supply while on the Treatment Phase of the study. Investigators should refer to the package insert for instructions regarding storage, handling, and administration of AAP.[64] AA will be provided as 4 x 250 mg tablets for a total dose of 1,000 mg for once daily oral administration, and prednisone will be provided as 5 mg tablets for twice daily oral administration (total daily dose of 10 mg). Niraparib will be provided as 2 x 100 mg capsules for once daily oral administration.

Subjects should take their daily dose of study drugs in the morning on an empty stomach. No food or liquids should be consumed for at least 2 hours before and for at least 1 hour after dosing. The study drugs should be swallowed whole with water. Study drugs should be administered together, except for prednisone, which may be taken at any time. If a subject forgets to take the study drugs at the regular time (eg, niraparib alone, AAP alone, or both), then the dose should be omitted. For treatment modifications due to toxicities see Section 6.2.

6.1.3. Combination 3: Niraparib/AA Fixed-dose Combination Tablet

See Attachment 6 for dosing instructions during the PK Assessment Phase.

See Section 6.1.2, above for dosing instructions during the Extension Phase.

6.2. Dose Modification and Management of Toxicity

All dose interruptions, discontinuations, and their reasons must be recorded in the eCRF. Management of toxicities for niraparib should be performed as detailed in Section 6.2.1. Management of toxicities for combination agents will be provided in the respective subsections from Section 6.2.1.2, onwards. Cycle days are fixed based on the Cycle 1 Day 1 date and will not change due to dose interruptions or delays.

The investigator should attempt to attribute the toxicity to niraparib or combination agent and adjust accordingly. If the toxicity cannot be attributed solely to niraparib or combination agent or both, then both study drugs should be interrupted. If either niraparib or combination agent is permanently discontinued for toxicity, the other drug may be continued after discussion with the sponsor.

Niraparib combination therapy should be held for at least 24 hours (or longer if specified for the combination agent) prior to significant procedures and should be resumed only when AEs related to the procedure are resolved. Any potential procedures should be discussed with the sponsor's medical monitor prior to the procedure occurring.

6.2.1. Combination 1: Niraparib and Cetrelimab

6.2.1.1. Combination 1: Dose Modifications for Niraparib

6.2.1.1.1. Non-hematological 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. If dose reduction is used for AE management, then please note that only 1 dose-level reduction will be permitted for niraparib (from 200 mg to 100 mg) (from 2 capsules to 1 capsule). Niraparib must be discontinued for non-hematologic treatment-related Grade ≥3 toxicities lasting more than 28 days while the subject is administered niraparib 100 mg once daily. Subjects experiencing treatment-related hypertensive crisis will have study drug permanently discontinued.

For Combination 1 only: If a subject has been escalated to niraparib 300 mg once daily, treatment must be interrupted for any non-hematological toxicity of Grade 3 or higher as above. However, if the toxicity resolves to Grade 1 or baseline, the subject should restart treatment with niraparib at 200 mg once daily and should not be re-escalated to the 300 mg dose. If the event recurs, the rules should be followed as for those subjects who start and are maintained on niraparib dose of 200 mg once daily, as described in the prior paragraph.

Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinicoradiological syndrome characterized by headache, seizures, altered mental status, visual loss and characterized by white matter vasogenic edema affecting the posterior and parietal lobes of the brain predominantly. Subjects who develop neurological symptoms suggestive for PRES should be immediately referred for neurological assessment and intake of niraparib interrupted. If diagnosis of PRES is confirmed, treatment with niraparib must be permanently discontinued. Blood pressure monitoring and correction if necessary is one of the cornerstones of PRES management.

6.2.1.1.2. Hematologic Toxicity

Dose interruption/modification criteria for platelet and neutrophil counts will be based on the criteria outlined in Table 4. For the management of anemia, supportive measures such as blood transfusions 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, niraparib should be interrupted until resolution to Grade <3 and discussed with sponsor prior to resuming treatment. Once the dose of study drugs has been reduced, any re-escalation must be discussed with the medical monitor.

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 prolonged period of dose interruption. Niraparib must be discontinued in case of inadequate recovery of platelet counts, neutrophil counts and/or hemoglobin to acceptable levels (Grade 1 or baseline) within 28 days of the dose interruption period, or if the subject has already undergone dose reduction to 100 mg once daily.
- A diagnosis of MDS/AML is confirmed by a hematologist. During the course of the study, subjects who receive a confirmed diagnosis of AML should discontinue niraparib. During the course of the study, subjects who receive a diagnosis of MDS confirmed by bone marrow biopsy and who require treatment for MDS beyond growth factor support and transfusions should discontinue niraparib. For subjects requiring no therapy or supportive care for MDS, continuation of niraparib treatment may be considered weighing the risk/benefit to the subject and must be discussed with the sponsor.

Table 4: Niraparib Dose Modification/Reductions for 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. If a subject had been escalated to niraparib 300 mg, resume niraparib at 300 mg or 200 mg.[b]
Grade ≥3	Interrupt until ≤Grade 1 or baseline, then: • 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 300 mg, restart at 200 mg.[a,b] • If subject was on 100 mg (because of non-hematologic toxicity), discuss with sponsor prior to resuming treatment. Weekly monitoring until resolution is required and recommended for 28 days after restarting dose.
Second occurrence Grade ≥3	Interrupt until ≤Grade 1 or baseline and restart at 1 dose-level reduction.[a] Weekly monitoring until resolution is required and recommended for 28 days after restarting dose. If subject was on 100 mg, (because of non-hematologic toxicity), discuss with sponsor prior to resuming treatment.
Third occurrence Grade ≥3	Permanently discontinue

a. For each dose level reduction, decrease dose by 100 mg or 1 capsule of niraparib.
b. Applies only to Combination 1. Only subjects in this combination may escalate to niraparib 300 mg (in specific instances).

Notes:

- For subjects with a platelet count ≤10,000 cells/μL, prophylactic platelet transfusion per guidelines may be considered. For subjects taking anticoagulant or antiplatelet therapy, consider the risk/benefit of interrupting these drugs or prophylactic transfusion at an alternative threshold such as ≤20,000 cells/μL.
- 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.
- 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.

6.2.1.2. Combination 1: Dose Modifications for Cetrelimab

6.2.1.2.1. Retreatment Criteria for Cetrelimab

Before each IV administration of cetrelimab, the subject will be evaluated for possible toxicities that may have occurred since the previous dose. Laboratory results and general physical status must be reviewed. If immune-related toxicity has occurred, the criteria outlined in Section 6.2.1.2.5, must be followed for management. Treatment with cetrelimab may continue unless the criteria for discontinuation of study drug in Section 10.2, are met. The criteria for retreatment are outlined in Table 5.

Table 5: Retreatment Criteria for Cetrelimab

Adverse Event	Requirements Before Each Study Agent Administration
ANC	≥1.0 x 10^9/L with or without neutrophil growth factors
Platelet count	≥50.0 x 10^9/L without platelet transfusions
Hemoglobin	≥7.5 g/dL with or without transfusion
Fasting glucose	≤250 mg/dL (13.9 mmol/L)
Hyperthyroidism	≤Grade 2
AST and ALT	≤3 x ULN
Total bilirubin	≤1.5 x ULN
Rash	≤Grade 2

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; ULN=upper limit of normal

6.2.1.2.2. Management of Infusion-related Reactions

Guidelines for the management of IRRs are described in Table 6. A reaction may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. IRRs should be graded per NCI-CTCAE criteria.

Table 6: Management and Follow-up of Infusion-related Reactions

For guidelines for delaying a dose, refer to Section 6.2.1.2.3.	
Grade 1	No intervention indicated; remain at bedside and monitor subject until recovery from symptoms, Consider diphenhydramine 50 mg (or equivalent) or paracetamol 325 to 1000 mg (acetaminophen) or both at least 30 minutes before additional study drug administration.
Grade 2	**Stop infusion**; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV or paracetamol 325 to 1000 mg (acetaminophen) or both; consider corticosteroids and bronchodilator therapy; remain at bedside and monitor subject until recovery from symptoms. **Restart infusion at 50% of initial rate:** if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. **Symptoms recur:** discontinue treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.
Grade 3-4	**Stop infusion**; start IV saline infusion, bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), or all 4, as needed.

For guidelines for delaying a dose, refer to Section 6.2.1.2.3.	
	Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
General	**Prophylactic medications (after initial event)**: diphenhydramine 50 mg (or equivalent) or paracetamol 325 to 1000 mg (acetaminophen) or both at least 30 minutes before additional study drug administrations; if necessary, corticosteroids (recommended dose: up to 80 mg of IV methylprednisolone or equivalent) may be used Appropriate resuscitation equipment should be available in the room and a physician readily available during the infusion of study drug.

6.2.1.2.3. Dose Delay for Cetrelimab

Dose delay is the primary method for managing cetrelimab-related toxicities. In the event of a toxicity that meets the criteria below or is otherwise considered to be clinically significant by the treating physician, treatment will be held and supportive therapy administered as clinically indicated. If clinically significant drug-related toxicity is present, treatment with cetrelimab should be delayed until the toxicity resolves (with or without supportive therapy) to baseline or Grade ≤1 except for alopecia, hyperthyroidism and rash, for which resolution to Grade ≤2 is required before subsequent treatment. If the toxicity does not resolve to Grade ≤1 or baseline within 12 weeks of identification of the toxicity, treatment discontinuation of cetrelimab is recommended unless otherwise agreed to by the sponsor medical monitor.

Dose delays are required for:

- Grade 2 pneumonitis (for recurrent Grade 2 or higher pneumonitis, study drug must be permanently discontinued)
- Grade 2 diarrhea or colitis
- Grade 3 creatinine elevation
- Grade 2 elevation in AST or ALT
- Grade 2 elevation in total bilirubin, except for subjects with Gilbert's syndrome (those subjects should have direct bilirubin measured and delay for Grade 2 elevation)
- Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, and diabetes)
- Grade 3 rash (maculopapular, aceniform, pustular, papulopustular)

The criteria for discontinuation of study treatment are described in Section 6.2.1.2.4, and Section 10.2.

6.2.1.2.4. Toxicities Leading to Discontinuation of Cetrelimab

A subject must discontinue study treatment for any of the following:

- The investigator believes that because of treatment-emergent toxicity, it is in the best interest of the subject to discontinue study treatment.
- Grade 4 toxicities except for endocrinopathies that are controlled with replacement hormones.
- Grade 2 or 3 immune-related AEs (irAEs) that persist despite treatment modifications or corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
- A treatment-related AE that does not resolve to Grade ≤1 within 12 weeks of the last dose of study drug unless otherwise agreed to by the sponsor medical monitor.
- Any non-hematological treatment-related event that occurs a second time at Grade ≥3 severity.
- Grade ≥3 (or recurrent Grade 2) pneumonitis.
- Grade ≥3 nephritis with creatinine ≥3 x ULN.
- Grade ≥3 elevation of AST or ALT or total bilirubin that does not resolve with supportive measures, as described in Attachment 1.
- Grade ≥3 IRRs.
- Immune-mediated encephalitis.

If a subject's treatment with cetrelimab is discontinued, this will not result in automatic withdrawal of the subject from the study. As above, the subject can continue niraparib if there is no evidence of disease progression and is otherwise tolerating treatment. Once a subject meets the cetrelimab discontinuation criteria, the subject may not be retreated with cetrelimab.

6.2.1.2.5. Guidelines for Management of Immune-related Adverse Events and Adverse Events of Clinical Interest for Cetrelimab

Therapy with immuno-oncology agents such as cetrelimab may lead to specific irAEs. Early recognition and management of these irAEs may mitigate more severe/subsequent toxicity. However, differential diagnoses, including non-inflammatory etiologies as well as the impact of the underlying malignant disease or concomitant medication, should be considered according to standard medical practice.

Algorithms have been developed to assist investigators in assessing and managing specific irAEs following administration of nivolumab[38] and pembrolizumab.[31] The guidelines specific to the management of cetrelimab are summarized as follows:

1. Subjects should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune-related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.

5. More potent immunosuppressives should be considered for events not responding to systemic corticosteroids (eg, anti-TNF agents or mycophenolate).

For management of individual toxicities, follow the guidance in Attachment 1.

6.2.2. Combination 2: Niraparib and AAP

Refer to Section 6.2.1.1, for niraparib dose modifications.

6.2.2.1. Combination 2: Dose Modifications for AAP

For Combination 2, once the dose of any study drug is reduced, any re-escalation to a full starting dose must be discussed in advance with the sponsor's medical monitor (with the exception of dose reduction for LFT-related toxicity, for which no dose re-escalation will be permitted, as discussed in Section 6.2.2.1.2).

In general, dose interruptions/modifications should be managed as follows:

- Grade 1 or Grade 2 toxicities should be managed symptomatically without requiring dose adjustments or dose interruptions; however, closer monitoring (laboratory or clinic visits) should be considered.
- The dose of prednisone can remain unchanged with dose modifications of niraparib or AA.

If either study drug is permanently discontinued due to toxicity, the other study drug (niraparib or AA) may be continued. Prednisone should be discontinued (with a taper if clinically indicated) if AA is permanently discontinued.

6.2.2.1.1. 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. If the toxicity cannot be definitively attributed to either niraparib only, then both niraparib and AA should be interrupted. If study drugs are to be restarted, then AA should be restarted first. If there is continued resolution of the AE to baseline/Grade 1, then niraparib may be restarted at least 7 days after restarting AA. If dose reduction is used for AE management, then please note the following:

- Only 1 dose-level reduction will be permitted for niraparib (from 200 mg to 100 mg) (from 2 capsules to 1 capsule).
- For AA, up to 2 dose-level reductions are permitted. At each dose-level reduction, the dose will be reduced by 1 tablet (250 mg) of AA, for example 4 to 3 tablets or 3 to 2 tablets.

6.2.2.1.2. Hepatic Toxicities

Hepatic toxicities are a known potential side effect of AAP and niraparib, but are more common with AAP treatment.[22,24] Table 7 provides dose recommendations for subjects who develop liver function test abnormalities during treatment with niraparib and AAP. During dose interruptions, LFTs should be monitored at least weekly. For Grade ≥2 liver function test (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 and then follow the Time and Events Schedule.

Table 7: Dose Modification Criteria for AST/ALT/Bilirubin Abnormalities for Niraparib and Abiraterone Acetate Plus Prednisone

Toxicity Grade	Dose of Niraparib	Dose of Abiraterone Acetate	Dose of Prednisone
Grade 1	No change.	No change.	No change.
Grade 2	No change.	No change.	No change.
Grade 3	Interrupt until return to baseline. Then, resume at previous dose at least 7 days after AA has been started without AST/ALT/bilirubin abnormalities and only after discussion and agreement with medical monitor. AST/ALT/bilirubin must be confirmed Grade 1 or baseline before restarting.	Interrupt until return to baseline or to AST or ALT ≤3 x ULN and total bilirubin ≤1.5 x ULN, resume at 750 mg (3 tablets) only after discussion and agreement with medical monitor.	No change.
Recurrence Grade 3	Interrupt until return to baseline. Then, resume at 1 dose-level reduction at least 7 days after AA has been started without AST/ALT/bilirubin abnormalities and only after discussion and agreement with medical monitor.	Interrupt until return to baseline or to AST or ALT ≤3 x ULN and total bilirubin ≤1.5 x ULN, resume at 500 mg (2 tablets) only after discussion and agreement with medical monitor.	No change.
Grade 4	Must be interrupted and discussed with medical monitor.[a]	Must be interrupted and discussed with medical monitor. [a]	No change or consider tapering if AA discontinued.

AA=abiraterone acetate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

[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 20 x ULN) anytime while receiving AA, subjects should be discontinued from treatment and retreatment with AA should not be attempted. Re-escalation of AA or 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 treatment with study drugs.

6.2.2.1.3. Hypokalemia

Hypokalemia is a known side effect of AAP.[22] Niraparib does not need to be interrupted/modified for hypokalemia.

For subjects who develop hypokalemia on study treatment, maintenance of the subject's potassium level at 4.0 mM or higher should be considered. If hypokalemia persists despite optimal potassium supplementation and adequate oral intake, the dose of prednisone may be increased by 5 mg/day and documented in the study medication eCRF. The increased dose of prednisone (or prednisolone) must be obtained locally from an open-label source (eg, a prescription provided by investigator) and documented as a concomitant medication. For Grade ≥3 hypokalemia, AA must be interrupted, and appropriate medical management instituted (eg, obtain ECG and provide potassium supplement). Treatment with AA should not be reinitiated until hypokalemia has resolved to Grade 1 or baseline.

6.2.2.1.4. Treatment Interruptions for Procedures

Both niraparib and AA should be held for at least 24 hours prior to procedures that require hospitalization. Study drugs should be resumed only when AEs related to the procedure are resolved. Prednisone can be continued during AA interruption.

6.2.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

Refer to Section 6.2.1.1, for niraparib dose modifications and Section 6.2.2.1, for AAP dose modifications.

6.3. Treatment of Overdose

For this study, any dose of niraparib, AA, niraparib/AA FDC, cetrelimab, or prednisone greater than the protocol-specified daily dose of study medication will be considered an overdose. This may also apply to increased exposure to AA arising due to the study medication being taken with food (ie, without fasting). Overdose is addressed in the niraparib (Zejula®), AA, and RAYOS product information[62,64,43] and in the cetrelimab IB[23] as:

- Niraparib: There is no specific treatment in the event of niraparib overdose. Physicians should follow general supportive measures, hold niraparib, and treat symptomatically. Serial complete blood counts should also be obtained.
- AA: There is no specific antidote. In the event of an overdose, stop AA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure, and assess liver function.
- Cetrelimab: There is no known specific antidote for overdose with cetrelimab. Treatment of overdose of cetrelimab should consist of general supportive care.
- Prednisone/prednisolone: Treatment of acute overdose is by immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the subject for AE/SAE and laboratory abnormalities until niraparib, AA, cetrelimab, or prednisone/prednisolone can no longer be detected systemically (at least 30 days).

- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

7. TREATMENT COMPLIANCE

For niraparib, a count of all capsules provided by the sponsor will be conducted during the Treatment Phase (Extension Phase for Combination 3) of this study. Niraparib will be dispensed and dosing compliance will be assessed at study visits as described in the relevant Time and Events Schedule: Attachment 5 (Combinations 1 and 2) and Attachment 6, Time and Events Schedule 1A (Combination 3). 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 drugs received, to whom dispensed (subject-by-subject accounting), and accounts of any study drugs accidentally or deliberately destroyed. For any study drugs taken orally, the amount of study drugs 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 drugs supplied, dispensed, and subsequently destroyed or returned to the sponsor or its representative (see also Section 14.5).

7.1. Combination 1: Niraparib and Cetrelimab

For cetrelimab, administration should be under the supervision of the investigator or qualified investigational site staff at study visits. The total volume of cetrelimab infused will be compared to the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering cetrelimab will be provided in the Site Investigational Product Preparation Manual (SIPPM).

7.2. Combination 2: Niraparib and AAP

For AAP, a count of all tablets provided by the sponsor will be conducted during the Treatment Phase of this study. AAP will be dispensed, and dosing compliance will be assessed at study visits as described in Attachment 5. 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.

8. PRIOR AND CONCOMITANT THERAPY

See Attachment 6 for Prior and Concomitant Therapy for Combination 3.

All previous therapies for prostate cancer must be collected. Concomitant therapies must be recorded throughout each combination study beginning with the signing of the ICF to the end-of-treatment (EoT) visit. In addition, concomitant medications for AEs and SAEs related to the study drugs must be recorded up to 100 days after the last dose of study drugs for Combination 1 and 30 days after the last dose of study drugs for Combination 2. For Combination 1 only, all non-steroidal anti-inflammatory drugs (NSAIDs; eg, celecoxib) and antibiotics used 30 days prior to signing the ICF at prescreening until the EoT visit should be collected and entered into the eCRF

(see Section 9.5.5). Note that bone-strengthening regimens are permitted if clinically indicated. If bone-strengthening agents are prescribed, the choice of agent is at the discretion of the investigator. All therapies different from the study drugs must also be recorded in the eCRF. For subjects who have not undergone orchiectomy, concurrent treatment with a GnRHa to maintain testosterone <50 ng/dL should be documented as a concomitant medication 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 investigational drug or device study during the Treatment Phase is prohibited.

8.1. Prohibited Concomitant Therapies

The sponsor must be notified of any instances in which prohibited therapies are administered. If the permissibility of a specific drug/treatment is in question, the sponsor should be contacted. Combination-specific prohibited therapies are provided in the respective subsections.

- Investigational agents other than study drugs
- Other PARP inhibitors
- Other anticancer therapies, excluding GnRHa
- Testosterone
- Radiotherapy (except as described in Section 10.2)
- Chemotherapy
- Radiopharmaceuticals such as radium-223 (^{223}Ra), strontium (^{89}Sr), samarium (^{153}Sm), or similar analogues
- Live virus vaccines

8.1.1. Combination 1: Niraparib and Cetrelimab

- Agents that target the androgen axis, other than GnRHa (eg, anti-androgens such as enzalutamide and apalutamide; CYP17 inhibitors such as abiraterone acetate with prednisone)
- Immunosuppressants (eg, cyclosporine, infliximab). However, the use of immunosuppressive medications for the management of irAEs, IRRs, or in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.

8.1.2. Combination 2: Niraparib and AAP

- Agents that target the androgen axis, other than GnRHa (eg, anti-androgens such as enzalutamide and apalutamide; CYP17 inhibitors such as ketoconazole)
- Diethylstilbestrol (DES) or similar estrogen receptor agonists
- Pomegranates and pomegranate juice
- Spironolactone

  Strong inducers of CYP3A4 (eg, rifampin)

8.2. Restricted Concomitant Medications

For the most current information regarding potential drug-drug interactions with niraparib or combination agents and concomitant study medication, refer to the latest version of the appropriate Investigator's Brochures.[22,24] Agents that can increase the risk of bleeding (anticoagulants and antiplatelet therapies) should be used with caution especially in subjects experiencing thrombocytopenia.

8.2.1. Combination 1: Niraparib and Cetrelimab

Not applicable for Combination 1.

8.2.2. Combination 2: Niraparib and AAP

Restrictions based on the drug interaction potential of niraparib with AAP are as follows:

- Substrates of CYP2D6: caution is advised when AA is administered with medicinal products activated by or metabolized by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolized by CYP2D6 should be considered. Examples of medicinal products metabolized by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter 3 products requiring CYP2D6 to form their active analgesic metabolites).
- Substrates of CYP2C8: In a CYP2C8 drug-drug interaction study in healthy subjects, the AUC of pioglitazone was increased by 46% when pioglitazone was administered with a single-dose of 1000 mg AA. Although these results indicate that no clinically meaningful increases in exposure are expected when AA is combined with drugs that are predominantly eliminated by CYP2C8, subjects should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index (eg, paclitaxel) if used concomitantly with AA.

For the most current information regarding potential drug-drug interactions with niraparib and AAP, refer to the latest versions of the Investigator's Brochure for niraparib and AA.[22,23] Additional information is provided in Attachment 4.

9. STUDY EVALUATIONS

See Attachment 6 and Section 9.1.2.3, below for Study Evaluations for Combination 3.

9.1. Study Procedures

9.1.1. Overview

Under Amendment 6, Time and Events Schedules 1 (Combination 1) and 3 (Combination 2) are superseded by Attachment 5; Time and Events Schedule 2 is obsolete.

The Time and Events Schedules summarize the frequency and timing of assessments applicable to this protocol and associated combination studies. If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, and any type of blood draw last. Blood collections for pharmacokinetic and immunogenicity assessments should be kept as close to the specified time as possible (Combination 1 only). Actual dates and times of assessments will be recorded in the source

documentation. Other measurements may be done earlier than specified timepoints if needed. Medical resource utilization data will also be collected. Refer to Section 9.6, Medical Resource Utilization for details.

For each subject, the planned maximum amount of blood drawn will not exceed 70 mL at any visit. Refer to the study 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.

The Long-term Extension Phase for the specified combination will start once the Amendment 7 has been approved at the site and after the notification by the sponsor (Attachment).

9.1.2. Prescreening Phase for Biomarker Evaluation

Subjects will be required to sign a prescreening specific ICF and provide baseline demographic information and disease-specific medical history. After signing the prescreening ICF, all subjects in Combinations 1 and 2 must have a blood sample collected to determine biomarker status, unless already eligible by a sponsor assay (Tissue may also be used to determine eligibility as described in Section 9.5). If a subject has been determined to be biomarker positive by sponsor approved assay with confirmation by sponsor review, a blood sample is still required. SAEs related to the blood collection procedure, as well as deaths from any cause, will be collected from the time the prescreening ICF is signed until 30 days after the procedure occurs (see Section 12.3.1). For Part 1 of the study, subjects may begin dosing prior to the results of biomarker assay becoming available. For Part 2 of the study, Subjects must have a result available prior to dosing. If the sample used to determine eligibility fails to produce a conclusive result, subjects may have testing performed again once.

9.1.2.1. Combination 1: Niraparib and Cetrelimab

For Combination 1, subjects will be assigned to a cohort based on their biomarker status (DRD [biallelic] or CDK12 pathogenic alteration).

9.1.2.2. Combination 2: Niraparib and AAP

For Combination 2, subjects will be eligible to proceed to the Screening Phase if determined to have DRD (see Section 9.5).

9.1.2.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

For Combination 3, biomarker status is not required to determine study eligibility. If not already known, biomarker status assessment is recommended, and results can be used to guide further treatment decisions during the Extension Phase (see Attachment 6).

9.1.3. Screening Phase

During this phase, eligibility criteria will be reviewed and evaluations performed as specified in Time and Events Schedules. Screening procedures may be performed within 28 days before Cycle 1 Day 1, unless otherwise specified. Imaging will be accepted up to 8 weeks prior to Cycle 1 Day 1. The screening physical exam, PSA and clinical safety laboratory evaluations can be used

for Cycle 1 Day 1 assessments if performed within 14 days of Cycle 1 Day 1. Details of screening laboratory tests are provided in Section 9.7, and Table 10. Assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained, provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to enrollment.

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

Subjects who do not meet all inclusion criteria, or who meet an exclusion criterion, may be rescreened once. Rescreening is at the discretion of the investigator and requires sponsor approval and agreement. 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, CT/MRI and bone scans (if still within 8 weeks of Cycle 1 Day 1) to determine eligibility if not the reason for the rescreening. All other rescreening and subsequent enrollment activities must be conducted in accordance with all protocol defined windows and timelines.

9.1.4. Treatment Phase

The Treatment Phase will begin at Cycle 1 Day 1 and will continue until the EoT visit. All site visits during the Treatment Phase will have a ±3-day window. Study visits will be calculated from the Cycle 1 Day 1 date. Refer to the Time and Events Schedules for treatment visits and assessments during the Treatment Phase.

For all site visits days and PK or immunogenicity sampling days (as applicable to each combination), the subject must not take niraparib at home in the morning; both study drugs should be administered at the investigational site. Details of PK or immunogenicity sampling days and times are provided in the Time and Events Schedule corresponding to the applicable combination. Additional details regarding PK or immunogenicity sampling (as applicable to each combination) are provided in Section 9.3. Details of blood sample handling and storage procedures for PK or immunogenicity are provided in each study Laboratory Manual.

Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. Treatment will continue until disease progression, unacceptable toxicity, death, or the sponsor terminates the study (see Section 10).

9.1.4.1. Long-term Extension Phase With Minimal Data Collection

After primary analysis of a combination, and the sponsor's subsequent decision and notification to limit further data collection, all subjects still in the Treatment Phase of that combination will be offered the option to enter the Long-term Extension Phase of the study. All subjects must sign the ICF for the Long-term Extension Phase before entering it. Details for the Long-term Extension Phase are provided in Attachment .

If niraparib or the combination-specific drug(s) are commercially available, subjects might be offered to change to the commercially available drug. If a dedicated Extension study or Post-Trial Access program becomes available, then all subjects who comply with the entry criteria for that study and consent to that study should be transferred to that study. In both scenarios, the subject will discontinue from the current study.

The Long-term Extension Phase for the specified combination will start once the Amendment 7 has been approved at the site and after the notification by the sponsor, sites will collect only the data specified in Attachment .

9.1.5. End-of-Treatment Visit

An EoT visit must be scheduled within 30 days after study drugs are discontinued, or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. Refer to the Time and Events Schedules for required assessments at the EoT visit. If a subject is unable to return to the site for the EoT visit, then the subject should be contacted to collect AEs or SAEs that occurred, and concomitant medications taken, within 100 days after the last dose of study drugs for Combination 1 and 30 days for Combinations 2 and 3, unless the subject received subsequent therapy, has died, is lost to follow-up, or has withdrawn consent. If the information on concomitant therapies and AEs is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents. If the subject dies, then the date and cause of death will be collected and documented in the eCRF.

Note that bone, CT, or MRI scans performed ≤6 weeks prior to the EoT visit may serve as EoT scans.

9.1.6. Follow-Up Phase

Once a subject has completed the Treatment Phase, deaths regardless of causality and SAEs thought to be related to study drugs, including associated concomitant medications, will be collected and reported within 24 hours of discovery or notification of the event. Related AEs should be reported as per the procedures in Section 12.3.1. 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.

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 (±2 weeks) until confirmed radiographic progression or initiation of subsequent therapy, provided the subject 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.

9.2. Antitumor Activity

9.2.1. Evaluations

Antitumor activity evaluations will be conducted as specified in the Time and Events Schedule for each combination. Unscheduled assessments should be considered if clinically indicated and results collected in the eCRF. The antitumor activity 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 the sponsor and these results will be used for the primary endpoint analyses.
- serum PSA
- CTCs
- survival status

For Combination 1 only: Evaluation of treatment response will also be assessed by the immune-related RECIST Criteria.[9]

9.2.2. Criteria

Objective response of soft tissue (visceral or nodal disease) is defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 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 for confirmation.

Radiographic progression by tumor assessment should be evaluated according to RECIST 1.1 for soft tissue disease and PCWG3 for bone disease (ie, to evaluate duration of response) 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. Under these criteria, any bone progression must be confirmed by a subsequent scan ≥6 weeks later. The Week 8 scan (first post-treatment scan) should be used as the reference scan to which all subsequent scans are compared to determine progression. Bone progression is defined as one of the following:

  1. Subject whose Week 8 scan is observed to have ≥2 new bone lesions compared to baseline scan will need to have a confirmatory scan performed ≥6 weeks later and would fall into one of the 2 categories below:

     a. Subject whose confirmatory scan (which is performed ≥6 weeks later) shows ≥2 new lesions compared to the Week 8 scan (ie, a total of ≥4 new lesions compared to 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 to the Week 8 scan will not be considered to have bone scan progression at that time. The Week 8 scan will be considered as the reference scan to which subsequent scans are compared.

  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 will be performed according to PCWG3 criteria.[50] Duration of tumor response will be assessed only for those subjects who have an objective tumor response by RECIST 1.1. 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).

See Section 10.2, for details regarding discontinuation of study medication for disease progression.

9.3. Pharmacokinetics and Immunogenicity (Combination 1)

As of Amendment 6, pharmacokinetic and immunogenicity assessments for Combination 1 are no longer being performed.

See Attachment 6 for pharmacokinetic assessments for Combination 3.

Blood samples will be collected to measure the plasma concentration of niraparib, and if performed, its metabolite, M1. Plasma or serum concentration of the combination agent, and immunogenicity (if applicable) will also be assessed. In addition, serum or plasma collected for PK or immunogenicity analyses may be used to evaluate safety or antitumor activity concerns arising during or after the study period. Genetic analyses will not be performed on these samples. Subject confidentiality will be maintained.

9.3.1. Sample Collection and Handling (Combination 1)

See the appropriate combination Time and Events Schedule for details of PK or immunogenicity sample collection (as applicable to each combination). Samples will be tested by the sponsor or sponsor's designee. The exact dates and times of blood sampling must be recorded. Refer to the study Laboratory Manual for sample collection requirements. Additional information about the collection, handling, and shipment of biological samples can be found in the study Laboratory Manual.

9.3.2. Analytical Procedures (Combination 1)

Plasma samples will be analyzed to determine concentrations of niraparib using a validated liquid chromatography/mass spectrometry (LC/MS) method by, or under the supervision of, the sponsor. If performed, the concentration of niraparib's M1 metabolite may be determined with a qualified or validated LC-MS method. Concentration of the combination agent (and immunogenicity, if applicable) will also be determined by a validated assay, as appropriate.

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).

9.3.2.1. Combination 1: Niraparib and Cetrelimab

Serum samples will be analyzed to determine the concentrations of cetrelimab and the generation of antibodies to cetrelimab using validated immunoassay methods. Other analyses may be performed to further verify the stability of antibodies to cetrelimab and/or characterize the immunogenicity of cetrelimab. Immunogenicity analysis may be conducted on PK samples collected at other time points, if deemed necessary.

9.3.3. Pharmacokinetic Parameters (Combination 1)

Plasma concentrations of niraparib and M1 (if performed) will be summarized by timepoint. Note: time zero is in reference to administration of niraparib or combination agent, as appropriate. Population PK parameters may be derived as appropriate. Concentration-time data may be combined with other studies and analyzed using a nonlinear mixed-effects modeling approach.

9.3.3.1. Combination 1: Niraparib and Cetrelimab

The following PK parameters will be calculated for cetrelimab as data permit:

- C_{max} maximum observed concentration
- t_{max} time to reach the maximum plasma concentration
- C_{trough} minimum observed (ie, predose) concentration following multiple dosing

9.4. Pharmacokinetic/Pharmacodynamic Evaluations (Combination 1 Only)

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

9.5. Biomarkers

All subjects in Combinations 1 and 2 must be evaluated for DRD and CDK12 before being enrolled into the study. Subjects must have DRD status assessed by the sponsor's required blood or tissue assays. CDK12 status will be assessed by tissue assay until blood assay becomes available. If previous local testing (by CLIA-certified or equivalent laboratory) shows DRD or CDK12 pathogenic alteration and result is reviewed by sponsor to confirm eligibility, subject may enter screening. However, blood and tissue should be collected and assessed for DRD and CDK12 by sponsor's required assays.

The biomarkers of interest for Combinations 1 and 2 are listed in Table 8. The criteria for cohort eligibility in Combination 1 and Combination 2 are listed in Table 9.

Table 8: 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[a]	Histone Deacetylase 2 gene
ATM	Ataxia Telangiectasia Mutated gene
CDK12[b]	Cyclin Dependent Kinase 12

a HDAC2 is only detected by the blood-based assay
b CDK12 is detected by the tumor assay and blood assay (once it becomes available)

Table 9: DRD and CDK12 Status and Cohort Eligibility in Combination 1 and Combination 2

DRD status (blood or tissue*)	Combination 1 Eligibility	Combination 2 Eligibility
BRCA biallelic loss	Cohort 1A	Cohort 2A
Other gene biallelic loss	Cohort 1A	Cohort 2B
CDK12 pathogenic alteration	Cohort 1A	Not applicable
BRCA monoallelic pathogenic loss	Not eligible	Cohort 2C
Other monoallelic pathogenic loss	Not eligible	Cohort 2D
Negative for DRD	Not eligible	Not eligible

Note: biomarkers are not collected for Combination 3.
* Once tissue algorithm is available for study use.

Biomarker status will not be required to determine study eligibility in Combination 3. If not already known, biomarker status assessment is recommended, and results can be used to guide further treatment decisions during the Extension Phase (see Attachment 6 for further information.)

On-study Biomarker Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical RRs. Biomarker analyses may be deferred or not performed, if during or at the end of the study, it becomes clear that the analyses will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event a combination is terminated early or shows poor antitumor activity, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before combination completion that additional material is needed from a tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

9.5.1. Tumor Samples

Tumor samples will not be collected in Combination 3.

Archival formalin-fixed paraffin-embedded tumor samples will be collected during Screening, if feasible. If unable to collect at Screening, archival tumor sample may be collected during Cycle 1.

Combination 1: Niraparib and Cetrelimab

Tumor samples may be used to examine proteins, RNA, and DNA biomarkers related to treatment response or resistance to treatment with the combination therapy and other immune-related or prostate cancer-related biomarkers.

These tumor biomarkers may include, but are not limited to, biomarkers that have been associated with response to PARP inhibitors, AR targeting agents, or anti-PD(L)-1 treatment, such as DRD,[35]

AR anomalies, mismatch repair,[34] PD-L1,[20,54] and tumor mutational burden.[42] PD-L1 expression will be retrospectively evaluated in tumor samples collected before, during and after treatment.

In this combination, fresh biopsies are mandatory at screening. Every effort should also be made to collect fresh biopsies at Cycle 1 Day 15 and EoT (if clinically feasible). Soft tissue biopsies are preferred; however, bone biopsies are allowed. The same organ system should be biopsied throughout the study, if clinically feasible.

9.5.2. Circulating Tumor Cells

Circulating tumor cells will not be evaluated in Combination 3.

Circulating tumor cells (CTCs) may be enumerated to determine CTC response to treatment and may be evaluated for gene and protein expression.

9.5.3. Circulating Tumor DNA- Combination 1 Only

Plasma-based circulating tumor DNA (ctDNA) will be evaluated for mutations in genes associated with DNA-damage response or CDK12 pathogenic alterations at the timepoints described in Time and Events Schedule 1. ctDNA may also be used to assess the presence of AR mutations, copy number changes, and other genes associated with resistance to niraparib combination therapy or prostate cancer disease biology.

9.5.4. Other Biomarker Assays

Other biomarker assays are not applicable for Combinations 2 and 3.

9.5.4.1. Combination 1: Niraparib and Cetrelimab

Whole blood samples may be examined by flow cytometry for markers of activated/effector T-cells, T-cell counts and other immune cell markers at the timepoints described in Time and Events Schedule 1 as part of immunophenotyping analysis. Peripheral blood mononuclear cells (PBMCs) may also be isolated from whole blood samples to obtain their derivatives (eg, RNA and DNA) and evaluated for immune-related, tumor type related, and other exploratory biomarkers (eg, alterations in gene expression, clonal T-cell expansion, or as germline reference for tumor-based genomic biomarkers). These biomarker analyses may include, but are not limited to, T-cell receptor sequencing, evaluation of mRNA expression of interferon-γ pathway genes, and gene signatures of T-cells and other immune cells. PBMC samples may also be used as reference samples for next generation sequencing analysis of tumor samples to determine if genetic alterations identified in tumor samples are somatic (ie, tumor specific). Blood samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers, such as cytokines, soluble PD-L1, mRNA expression of PD-L1 and other immune- or tumor-related biomarkers.

9.5.5. Non-steroidal Anti-inflammatory Drugs and Antibiotics (Combination 1)

Use of NSAIDs and antibiotics will be collected to explore whether subjects who have recently taken these agents may have changes to the tumor microenvironment, which may result in a

different response to the study drugs.[27,63] Collection of NSAID and antibiotic use will be from 30 days prior to screening until the EoT visit.

9.6. Medical Resource Utilization

Medical resource utilization information will not be collected in Combination 3.

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 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)

9.7. Safety Evaluations

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, clinical safety laboratory tests, ECOG PS, and other safety evaluations at specified timepoints as described in the Time and Events Schedule for each combination: Attachment 5 (Combinations 1 and 2), and Time and Events Schedule 1A in Attachment 6 (Combination 3). Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

Adverse Events

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.

Clinical Safety Laboratory Tests

Clinical Safety Laboratory Tests for Combination 3 are in Attachment 6.

Blood samples to assess the safety and antitumor activity of study drugs 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.

Tests will be performed at the timepoints outlined in Time and Events Schedule. Required laboratory tests must be performed within ±3 days of the scheduled visit during the Treatment Phase (windows of ±5 days and ±2 weeks are applicable at the EoT visit and during the Follow-up Phase, respectively). During Cycle 1, complete blood counts (CBCs) must be performed weekly and then as per the timepoints described in the Time and Events Schedule. In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required. Screening laboratory tests will be performed by the central laboratory and are detailed in Table 10. Clinical safety laboratory tests during the Treatment Phase and at EoT will be performed using local laboratories and are detailed in Table 11.

For suspected MDS/AML while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes) at screening. If needed, cytogenetic analysis will be done centrally for standardized evaluation. Testing completed as part of standard-of-care is sufficient if 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,[57] 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.

Table 10: Screening Laboratory Tests (Central Laboratory)

Hematology Panel		
-CBC (hemoglobin, white blood cell count, platelets, absolute lymphocyte count, and ANC)		
Serum Chemistry Panel		
-creatinine -potassium[b]	-lactate dehydrogenase	-glucose[a]
Liver Function Tests		
-AST -serum total bilirubin (if abnormal, measure direct bilirubin)	-alkaline phosphatase	-ALT
Other Laboratory Tests		
-testosterone -PSA[d] -serology (HIV and CD4 count if indicated[e], HBsAg, HepB core antibody, HCV antibody)	-TSH[c] -urinalysis[c]	-HgbA1c[c] -serum albumin

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CBC=complete blood count; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HgbA1c=hemoglobin A1c; HIV=human immunodeficiency virus; TSH=thyroid-stimulating hormone
Note: all screening laboratory tests may also be performed during the study as clinically indicated. Tests will be performed at the central laboratory.

[a] Fasting glucose in Combination 2.
[b] Potassium for Combination 2 only.
[c] TSH, HgbA1c, and urinalysis for Combination 1 only.
[d] PSA is tested at screening and as per the timepoints detailed in Time and Events Schedule.
[e] HIV and CD4 count should be only performed if indicated by prior medical history.

Table 11: Clinical Safety Laboratory Tests (Central or Local Laboratory)

Hematology Panel		
-CBC (hemoglobin, white blood cell count, platelets, absolute lymphocyte count, and ANC)		
Serum Chemistry Panel		
-creatinine	-lactate dehydrogenase	- glucose[a]
-potassium[b]		
Liver Function Tests		
-AST	-alkaline phosphatase	-ALT
-total bilirubin (if abnormal, measure direct bilirubin)		

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CBC=complete blood count
Note: all clinical safety laboratory tests may be performed more frequently during the study as clinically indicated. Tests will be performed at the central or local laboratory.
[a] Fasting glucose in Combination 1 and fasting glucose in Combination 2.
[b] Potassium for Combination 2 only

Electrocardiogram (ECG)

ECGs (12-lead) will be recorded at screening. Any known electrolyte imbalance should be treated prior to performing the ECG. Subjects are to reside in a quiet setting without distractions (eg, television, cell phones, and staff talking) 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.

Vital Signs

Body temperature, heart rate, and blood pressure will be recorded at the timepoints outlined in Time and Events Schedules. As hypertension has been reported with niraparib, blood pressure should be monitored weekly during the first 2 months of treatment (Cycles 1-2), and then monthly thereafter. Blood pressure monitoring can occur at clinic visit or may also be reported to the site by the subject, by home nurse, or by other method deemed reliable by the investigator. Follow the instructions in Section 6.1.1, for vital sign assessments during cetrelimab infusion.

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 2) 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 for each combination.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to Time and Events Schedules for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the study Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the study Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

See Attachment 6 for instructions on Completion, Discontinuation of Study Treatment, and Withdrawal from Study for Combination 3.

10.1. Completion

A subject will be considered to have completed the combination study if assessments have been completed through the end of the Follow-up Phase. A subject will be considered to have completed the Treatment Phase when study drug is discontinued for any reason. A safety follow-up visit should be planned.

10.2. Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the combination study if they discontinue the study drugs. Subjects who discontinue the study drugs should complete the EoT visit within 30 days of the last dose of study drug or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. Subjects should ordinarily be maintained on niraparib combination therapy 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 niraparib combination therapy at the investigator's discretion. Niraparib combination therapy will be continued for subjects who have increasing PSA values in the absence of radiographic or unequivocal clinical progression. Although serial PSA values 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 combination therapy.[50] However, a subject's niraparib combination therapy must be discontinued for:

- Combination drug-related toxicity as defined in Section 6.2.
- Unequivocal clinical progression defined as one or more of the following:

  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.
- 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 the study drugs for any reason remain on study and must follow all study evaluations described in Section 9, and outlined in the applicable Time and Events Schedules. Study data for survival and subsequent therapies will continue to be collected after discontinuation of treatment, unless the subject withdraws consent for further study participation.

In the event of early study completion or study termination by the sponsor, (whether or not the study endpoints are met), the sponsor will continue to provide study treatments until unequivocal disease progression, unacceptable toxicity, or an alternate method is in place to avoid treatment interruption.

10.3. Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent for subsequent data collection
- Combination 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. The informed consent will stipulate that even if a subject decides to discontinue the study drugs, the subject will agree to be contacted periodically by the investigator to assess endpoint status and for collection of safety data as per the Time and Events Schedule for each combination. This can be done by telephone or by chart review. If the subject withdraws consent for all study-related procedures, then no further contact is permitted by the investigator or the sponsor.

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

10.4. Withdrawal from the Use of Research Samples

The subject may withdraw consent for use of samples for 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 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 antitumor activity and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

A general description of the statistical methods for Combination 3 is in Attachment 6 (except for safety analysis).

11.1. Analysis Populations

All analysis populations are applicable to each combination.

Intent-to-Treat (ITT) Population: All subjects who are enrolled into a combination study and have at least 1 dose of both study drugs at the selected RP2D.

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

Pharmacokinetics Populations (PK): Subjects who have received at least 1 dose of both study drugs and have at least 1 concentration value. PK population is for Combination 1 only.

Continuous variables will be summarized using descriptive statistics such as mean, median, standard deviation (SD), and range. Categorical variables will be summarized using frequency tables.

11.2. Sample Size Determination

11.2.1. Combination 1: Niraparib and Cetrelimab

For Part 1 of the study, at least 6 evaluable subjects (defined in Section 3.1) will initially be enrolled. Additional dose regimens may be enrolled as discussed in Section 3.1.1. Non-evaluable subjects will be replaced.

For Part 2 of the study, approximately 30 subjects per cohort (ie, Cohort 1A BM+ or Cohort 1B BM-) were to be enrolled. However, a futility analysis was performed for Cohort 1B after approximately 10 subjects have been enrolled and evaluated (see Section 11.10). It is anticipated that the final analysis for the primary endpoint of ORR (defined in Section 11.3) will occur approximately 6 months after the last subject in each cohort is enrolled. Note that Cohorts 1A and 1B will be evaluated and analyzed independently.

As described in Section 1.1, there is limited data with single-agent PARP inhibitors for the treatment of mCRPC. The statistical assumptions are derived from the TOPARP study in which 6 out of 32 subjects with measurable disease had a confirmed radiologic response.[35] However, these results included data from subjects who were BM-, so the actual response rate for BM+ subjects is potentially higher. The response rate for anti-PD-1 agents in mCRPC is unknown; however, a minimal single agent response rate (5% to 10%) is estimated. Therefore, for this combination to be considered clinically meaningful, the observed response rate should be higher than the additive response of each treatment alone, thus a response rate of greater than 50% was established.

For Cohort 1A, the null hypothesis that the ORR is ≤25% will be tested against the alternative hypothesis that the ORR is ≥50%. Antitumor activity of niraparib and cetrelimab will be declared if the lower bound of the 2-sided 90% exact confidence interval (CI) for ORR is >25%. With approximately 30 BM+ subjects, Cohort 1A will have over 80% power such that the lower limit of the 90% CI for ORR exceeds 25%.

The response rate from the TOPARP study for single agent olaparib in prostate cancer is based on 1 subject with measurable disease who had a response, despite being BM-. The single-agent activity of niraparib is likely around 5% and the single-agent activity of anti-PD-1 in this population is similar to the BM+ population at 5% to 10%. Therefore, for this combination to be considered clinically meaningful, the response rate should be at least as efficacious as a chemotherapy-type regimen in this setting, hence a response rate of 30% was selected.

For Cohort 1B, the null hypothesis that the ORR is ≤10% will be tested against the alternative hypothesis that the ORR is ≥30%. Antitumor activity of niraparib and cetrelimab will be declared if the lower bound of the 2-sided 90% exact CI for ORR is >10%.[49] With approximately 30 BM- subjects, Cohort 1B will have over 80% power such that the lower limit of the 90% CI for ORR exceeds 10%.

11.2.2. Combination 2: Niraparib and AAP

For Combination 2, approximately 20 subjects per cohort will be enrolled; It is anticipated that the final analysis for the primary endpoint of response rate (defined in Section 11.3) will occur approximately 6 months after the last subject is enrolled.

As described in Section 1, there is limited data with single-agent PARP inhibitors for the treatment of mCRPC.

In a study of mCRPC subjects treated with olaparib, a composite response rate of 33% was observed regardless of biomarker status.[35] Subjects with mCRPC who have DRD may have greater benefit from the combination of Niraparib and AAP. For Cohort 2A and 2B the null hypothesis of composite response rate ≤33% will be tested against the alternative hypothesis of composite response rate ≥62%. Antitumor activity of niraparib and AAP for Cohort 2A (or 2B) will be declared if the lower bound of the 2 sided 90% exact confidence interval (CI) for the composite response rate is >33%. With approximately 20 subjects in Cohort 2A (or 2B), it will have over 80% power such that the lower limit of the 90% CI for the composite response rate exceeds 33%.

Based on the proposed mechanism of action of PARP inhibitors, subjects whose tumors have only monoallelic loss of a DRD gene may not have as robust a response to treatment as those with biallelic loss.[9] Therefore, for Cohort 2C and 2D the null hypothesis that the composite response rate ≤28% will be tested against the alternative hypothesis of composite response rate ≥57%. Antitumor activity of niraparib and AAP for Cohort 2C (or 2D) will be declared if the lower bound of the 2 sided 90% exact confidence interval (CI) for the composite response rate is >28%. With approximately 20 subjects in Cohorts 2C (or 2D), it will have over 80% power such that the lower limit of the 90% CI for the composite response rate exceeds 28%.

11.2.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

See Attachment 6 for sample size determination for Combination 3.

11.3. Antitumor Activity Analyses

11.3.1. Combination 1: Niraparib and Cetrelimab

Primary Endpoint

Subjects dosed during Part 1 at the selected RP2D combination will be included as part of the ITT Population.

The primary endpoint for Part 2 is ORR, defined as the proportion of subjects who achieve CR or PR determined by RECIST 1.1 criteria with no evidence of bone progression according to PCWG3 criteria. The analysis of primary endpoint will be performed based on the ITT Population, and ORR will be presented along with a 90% 2-sided exact CI.

Secondary Endpoints

The analyses for secondary endpoints will be performed based on the ITT Population.

- RR will be reported along with a 90% 2-sided exact CI.
- The distribution of OS will be summarized using the Kaplan-Meier method.
- CTC response rate will be presented with a 90% 2-sided exact CI.

Exploratory analyses only will be performed on efficacy data collected from subjects enrolled in this combination, pending data availability. Details will be provided in the SAP.

11.3.2. Combination 2: Niraparib and AAP

The primary endpoint for Combination 2 is composite response rate, defined as the proportion of subjects who have a composite response. The composite response is defined as 1 of the following by PCWG3:

- Objective response (confirmed per RECIST 1.1), or
- CTC response: defined as CTC 0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later, or

- PSA decline of ≥50%, measured twice 3 to 4 weeks apart.

The analysis of primary endpoint will be performed based on the subjects who receive Combination 2 in the ITT Population, and composite response rate will be presented along with a 90% 2-sided exact CI.

The analyses of secondary endpoints for Combination 2 will be performed based on the subjects who receive Combination 2 in the ITT Population.

- ORR will be reported along with a 90% 2-sided exact CI.
- CTC response rate will be presented with a 90% 2-sided exact CI.

Exploratory analyses only will be performed on efficacy data collected from subjects enrolled in this combination, pending data availability. Details will be provided in the statistical analysis plan (SAP).

11.3.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

Antitumor activity will not be assessed in Combination 3.

11.4. Pharmacokinetic and Immunogenicity Analyses (Combination 1 Only)

Plasma concentration-time data of niraparib, and its metabolite, as appropriate, will be summarized using descriptive statistics. Population PK analysis may be performed using nonlinear mixed-effects modeling for niraparib combination therapy. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Plasma or serum concentration-time data of the combination agent will be summarized using descriptive statistics. The incidence of anti-combination agent antibodies (if applicable) will be summarized for all subjects who receive at least 1 dose of combination agent and have appropriate samples for detection of antibodies to the combination agent (ie, subjects with at least 1 sample obtained after their first dose of combination agent). In addition, subjects who are positive for anti-drug antibodies (if applicable) will be listed. Other immunogenicity analyses may be performed to further characterize the immune responses that are generated (if applicable).

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for niraparib combination and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all subjects with available plasma/serum concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each treatment group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of niraparib, its M1 metabolite (if performed), and combination agents, as applicable.

11.5. Biomarker Analyses

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Appropriate details of these exploratory analyses will be included in the biomarker Statistical Analysis Plan for each combination and results will be presented in a separate report.

11.6. Pharmacokinetic/Pharmacodynamic Analyses (Combination 1)

If sufficient data are available, then other PK/pharmacodynamic modeling may be performed, including exploring the relationship between systemic (plasma or serum) concentrations of niraparib and combination agent, and endpoints of antitumor activity and safety. If performed, details and results of the analysis will be presented in a separate report.

11.7. Medical Resource Utilization

This does not apply to Combination 3.

The analysis will be prepared separately and will not be a part of the CSR.

11.8. Safety Analyses

Treatment-emergent AEs will be coded using the most current Medical Dictionary for Regulatory Activities and will be graded according to the NCI-CTCAE, Version 4.03 or later. Treatment-emergent AEs are those events that occur or worsen on or after first dose of study drug through 100 days after the last dose of study drugs for Combination 1 and 30 days after the last dose of study drugs for Combinations 2 and 3, or prior to administration of a subsequent therapy, whichever occurs first, and will be included in the analysis. AEs will be summarized by System Organ Class and Preferred Term and will be presented overall and by treatment group. 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.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint as appropriate. Parameters with predefined toxicity grades will be summarized. Change from baseline to the worst grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized. The percentage of subjects with clinically important changes from baseline will be summarized.

Physical Examination

Clinically relevant abnormalities observed during the physical examination will be recorded and summarized as AEs.

11.9. Data Review Committee

This does not apply to Combination 3.

For each combination, a DRC will be established to monitor data from Part 2 on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study. The committee will meet at least every 6 months to review interim data. After the review, the DRC will make recommendations regarding the continuation of the combination. The details will be provided in a separate DRC charter, which will be provided to the DRC members.

The DRC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The DRC responsibilities, authorities, and procedures will be documented in its charter.

11.10. Futility Analysis

The interim analysis of BA in Combination 3 is described in Attachment 6.

For Combination 1, a futility analysis (based on a Simon 2-stage design) was to be performed for Cohort 1B when approximately 10 BM- subjects are enrolled in Part 2 of the study. Further enrollment into the BM- cohort was to be held while the futility analysis was performed. If the response rate is 13% or less (ie, 0 or 1 responders) for the subjects included in the futility analysis, then the cohort was to close, otherwise the cohort was to be fully enrolled with approximately 30 subjects (see Section 11.2.1).

The pre-planned futility analysis was recently performed on the biomarker negative subjects (Cohort 1B) enrolled in phase 2 of niraparib + cetrelimab of the QUEST study. Based on the analysis conducted, a response rate of 13% was not achieved. Accordingly, the biomarker negative cohort (Cohort 1B) was closed to new enrollment. Subjects that are enrolled in this cohort and still on study may continue without any change to their status.

No futility analysis was planned for Combination 1 Cohort 1A. However, a DRC meeting was held after 18 subjects enrolled in Combination 1A. The ORR for the 18 subjects enrolled was 22% (95% confidence interval: 8%, 44%). Based on the current response rate, the chance of obtaining a 50% response rate in Combination 1A as hypothesized in the protocol by completing the cohort (n 30) is <1%. The DRC recommended closing enrollment of Combination 1A based on the low probability of success.

12. ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and Product Quality Complaints (PQC), 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.

Safety reporting requirements for subjects in Combination 1 or 2 are outlined in Attachment 5, and for Combination 3 are outlined in Attachment 6.

12.1. Definitions

12.1.1. Adverse Event and Serious Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a pharmaceutical (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 Council for 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 starting with the signing of the ICF (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.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

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 and other combination agents, the expectedness of an AE will be determined by whether or not it is listed in the respective Investigator's Brochure. For other combination agents that may have a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

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, accidental, or occupational exposure to a sponsor study drug
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without subject/patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

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 adverse event 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 ICF is obtained until completion of the subject's last study-related

procedure, which may include contact for follow-up of safety. For Combination 3, all AEs and SAEs will be reported from the time a signed and dated ICF is obtained through the PK Assessment Phase. Only SAEs will be reported under Amendment 4 for Combination 2 and during the Extension Phase of Combination 3 (after the 168-hour PK sampling on Day 8).

SAEs, including those spontaneously reported to the investigator within 100 days after the last dose of study drugs for Combination 1 and 30 days after the last dose of study drugs for Combinations 2 and 3, must be reported using the Serious Adverse Event Form. In addition, SAEs related to the blood collection procedure, as well as death from any cause, during the Prescreening Phase will also be reported from the time the ICF is signed until 30 days after the procedure occurs. 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 enter the Screening Phase, 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 an 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 3.

All AEs, regardless of seriousness, severity, or presumed relationship to study drugs, 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). 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, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee (IEC)/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, 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, as well as PQC, 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) or email. Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

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 drugs 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).
- A standard procedure for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).

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 antitumor activity 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 100 days after the last dose of study drugs for Combination 1 and 30 days after the last dose of study drugs for Combinations 2 and 3, must be reported using the Serious Adverse Event Form. SAEs that occur after 100 days following the last administration of study drugs for Combination 1 and 30 days after the last dose of study drugs for Combinations 2 and 3, which are thought to be related to the study drugs, will be collected and reported via the Serious Adverse Event Form within 24 hours of discovery or notification of the event and documented per standard procedures.

12.3.3. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

Solicited AEs

Solicited AEs are predefined local and systemic events for which the subject is specifically questioned.

Unsolicited AEs

Unsolicited AEs are all adverse events for which the subject is not specifically questioned.

12.3.4. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. Adverse events, including pregnancy, will be followed by the investigator as specified in Sections 12.3, and 13.

12.3.5. Pregnancy

While the effect of niraparib on sperm is unknown, PARP inhibitors disrupt DNA-repair of dividing cells and niraparib was observed to be genotoxic in in vitro studies.[24] Therefore, pregnancy is contraindicated and 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. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using

the Serious Adverse Event Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.6. Disease Progression and Death

It is anticipated that a proportion of subjects will experience disease progression, which will not by itself be considered as an AE, even if it results in death during the AE reporting period. If other AEs/SAEs occur in relation to disease progression, then those AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 12.3.1, All Adverse Events and Section 12.3.2, Serious Adverse Events, respectively.

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 100 days after the last dose of both study drugs for Combination 1 and 30 days after the last dose of study drugs for Combinations 2 and 3. Death is an outcome of an AE and not an AE itself. All reports of death within the reporting period should include an AE term for the cause of death (if known). Fatal events occurring after the reporting period will not be reported as SAEs and will be captured on the designated case report form.

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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and antitumor activity of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system. 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 under the correct storage conditions until a shipment request is received from 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

See Attachment 6 for Study Drug Information for Combination 3.

14.1. Physical Description of Study Drug(s)

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.[24]

14.1.1. Combination 1: Niraparib and Cetrelimab

Manufacturing changes to the cetrelimab drug substance and drug product may occur during this study. The drug product may be changed from a frozen liquid in vial to a lyophilized drug product. The host-cell line and the core amino acid sequence of the cetrelimab mAb remains unchanged for the frozen and lyophilized product. Comprehensive nonclinical comparability studies will be performed to assess the biochemical, biophysical, and biological characteristics of the lyophilized drug product to ensure that there is no impact on subject safety and product quality. The drug substance and drug product manufacturing changes, along with the results of the comparability studies will be submitted to the health authorities prior to introduction of the lyophilized product into the clinical program. The transition will happen as logistically allowed by the study.

Frozen Liquid in Vial

The cetrelimab frozen formulation is a sterile, frozen liquid in an 8R glass vial with serum stopper and aluminum seal with flip-off cap. Each vial of cetrelimab clinical study material is filled with 3.3 mL of a 10 mg/mL solution of cetrelimab (including 10% overfill).

Lyophilized

cetrelimab is supplied as a single-use, lyophilized product. cetrelimab final labeled product contains 3.3 mL at 30 mg/mL. The dosage form includes a 10% overfill and has been designed to deliver 90 mg of cetrelimab per vial. Cetrelimab is presented in an 8R glass vial with a 20 mm Coated Lyo stopper and 20 mm flip-off seal.

Both drug products will be manufactured and provided under the responsibility of the sponsor. Refer to the cetrelimab IB for a list of excipients for both the frozen liquid and lyophilized drug products.[22]

14.1.2. Combination 2: Niraparib and AAP

The AA tablet supplied for this study contains 250 mg of AA. Refer to the Investigator's Brochure for a list of excipients.[22] Prednisone tablets containing 5 mg prednisone will be provided directly by the sponsor.

14.2. Packaging

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

14.2.1. Combination 1: Niraparib and Cetrelimab

Cetrelimab vials will be packaged in kits (cartons). The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. cetrelimab vials will not be dispensed in child-resistant packaging.

14.2.2. Combination 2: Niraparib and AAP

AA 250 mg tablets will be packaged in high-density polyethylene bottles with child-resistant closures. Prednisone tablets will be packaged in blister packs or bottles.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

Refer to the pharmacy manual/study-site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

The study drugs 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 all medications out of reach and sight of children.

14.4.1. Niraparib

Niraparib may have adverse effects on a fetus in utero. Caregivers should handle niraparib with protection (eg, gloves). Study-site personnel will instruct subjects on how to store niraparib for at-home use as indicated for this protocol.

14.4.2. Cetrelimab

Cetrelimab 10 mg/mL must be stored frozen at controlled temperatures and protected from light. Specific storage temperature conditions will be provided separately. Protection from light is not required during infusion. Cetrelimab will be administered at the study site by study-site personnel using the guidelines provided in the pharmacy manual. Refer to the SIPPM for additional guidance on cetrelimab 10 mg/mL preparation, handling, and storage.

14.4.3. Abiraterone Acetate

AA is contraindicated in women who are or may potentially be pregnant. There are no human data

on the use of AA in pregnancy. Maternal use of CYP17 inhibitor is expected to produce changes in hormonal levels that may affect the development of the fetus. Women who are pregnant or may be pregnant should not handle AA without protection (eg, gloves). In an oral developmental toxicity study in the rat, abiraterone acetate affected pregnancy.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drugs received at the site are inventoried and accounted for throughout the study. The dispensing of study drugs to the subject, and the return of study drugs 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 drugs. All study drugs will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drugs containers. Any study drug administered to the subject must be documented on the drug accountability form.

Study drugs 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 drugs, and study drugs 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 drugs, or used returned study drugs 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 drugs 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 drugs will be supplied only to subjects participating in the study. Returned study drugs must not be dispensed again, even to the same subject. Whenever a subject brings his study drugs to the study site for pill count, this is not seen as a return of supplies. Study drugs may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drugs from, nor store them 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:

- Study protocol
- Investigator's Brochure
- Electronic data capture (eDC) manual
- SIPPM/study-site investigational product and procedures manual
- IWRS manual
- Pharmacy manual
- Sample ICFs
- Laboratory manual
- NCI-CTCAE Version 4.03 (or later)
- PCWG3 guidelines
- RECIST guidelines, version 1.1

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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.

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 will be designed to collect the minimum number of blood samples that can determine the safety, antitumor activity, PK, pharmacodynamics, 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.[60]

16.1.1. Combination 1: Niraparib and Cetrelimab

This is an open-label study to assess the safety, antitumor activity, PK, and determine the RP2D of niraparib when dosed in combination with cetrelimab, in subjects with prostate cancer over the age of 18 years, with and without DRD or CDK12 pathogenic alteration. Given that there remains a high unmet need for treatment of prostate cancer in patients who are refractory to available therapies and that the adverse effect profile of these therapies together is likely to be manageable, the sponsor considers that the benefit of treatment with niraparib in combination with cetrelimab outweighs the potential risks involved (as described in Section 1.4.1).

16.1.2. Combination 2: Niraparib and AAP

This is an open-label study to assess the safety and antitumor activity of 200 mg niraparib when dosed in combination with 1,000 mg AA and 10 mg (2 x 5 mg) prednisone, in subjects over the age of 18 years with metastatic prostate cancer. The potential benefits of treatment with niraparib and AAP in men with metastatic prostate cancer, both with and without prospectively selected DRD, outweighs the potential risks involved as described in Section 1.4.2.

16.1.3. Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

This is an open-label study to assess the relative BA of FDC tablet formulations of niraparib and AA, in subjects over the age of 18 years with metastatic prostate cancer. During the PK Assessment Phase, all subjects will receive 200 mg niraparib in combination with 1,000 mg AA and 10 mg prednisone (as SAs). Analysis of safety data from Cohort 2 (no HRR gene alterations) of the MAGNITUDE Study (see Section 1.4.3) supports treatment of subjects with metastatic prostate cancer and no HRR gene alterations with niraparib plus AAP for approximately 22 days.

The results of the futility analysis of the MAGNITUDE Study (see Section 1.1.2) did not show additional benefit of adding niraparib to AAP in subjects with no HRR gene alterations. Therefore, during the Extension Phase of this study, subjects with HRR gene alterations will be recommended to continue combination treatment with AAP and niraparib, and subjects without HRR gene alterations may continue therapy with AAP plus niraparib or AAP at the investigator's discretion guided by biomarker status. The potential benefits of treatment with niraparib and AAP in men with metastatic prostate cancer with prospectively selected HRR gene alterations outweigh the potential risks involved as described in Section 1.4.2

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 give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed 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. Informed consent may be obtained remotely. Refer to local applicable guidelines to ensure compliance. 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.

There are two informed consent forms (ICFs) for this study, one for prescreening (biomarker testing) and one for entry into the study. 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 physician may also recontact the subject for the purpose of obtaining consent to collect information about his survival status.

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. Where local regulations require, a separate ICF may be used for the required DNA component of the study.

In accordance with local regulations, all subjects enrolled in the study will be required to sign an updated informed consent form to continue in the study under Amendment 6.

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 or her 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 or her 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, pharmacogenomics, biomarker, and PK 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 and other therapies, to understand prostate cancer, to understand differential drug responders, and to develop tests/assays related to niraparib and other therapies and prostate cancer. 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 (refer to Section 10.4, Withdrawal From the Use of Samples in Future 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 age at initial informed consent. In cases where the subject is not enrolled into the study, the date seen and age at initial informed consent 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 documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care 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 antitumor activity 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; 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.

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 4.1, Prescreening Eligibility Criteria, Section 4.1.1, Inclusion Criteria, and Section 4.2.1, 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 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 eCRF 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 eCRF 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

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. Further information on the reporting of data from each combination can be found in Section 3.1.

17.9.2. Study Termination

The sponsor reserves the right to close the study site, close an individual cohort or combination arm, or terminate the study at any time for any reason at the sole discretion of the sponsor. If the sponsor decides to close a cohort, this will be communicated through a letter to the investigator. 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 other combination agents 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 other combination agents, 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 CSR 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 CSR has been issued will be reported in a separate report and will not require a revision of the CSR. 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 (ICMJE) 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 of the availability of the final data (tables, listings, graphs), 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 the important intellectual content; and given final approval of the version to the 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.

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Attachment 1: Combination 1: Guidelines for the Management of Immune-related Adverse Events for Cetrelimab

Management of Immune-Related Gastrointestinal Adverse Events

For guidelines for delaying a dose, refer to Section 6.2.1.2.3	
Grade 1	Symptomatic treatment according to institutional standards Close monitoring; instruct subject to report worsening immediately and treat as Grade ≥2
Grade 2	**≤5 days:** Symptomatic treatment according to institutional standards **>5 days or recurrence:** 0.5–1.0 mg/kg/d methylprednisolone; consider prophylactic antibiotics; **Persistence or worsening despite steroids >3 days:** treat as Grade 3/4 **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4	**Immediately:** 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower endoscopy **Persistence >3 days or recurrence:** add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) **Improvement to ≤Grade 2 within ≤3 days:** taper steroids over at least 4 weeks
General	The oral corticosteroid equivalent of the recommended IV dose may be considered for ambulatory patients; the lower bioavailability of oral corticosteroids needs to be considered. Clinical caution should be exercised, for subjects receiving concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, monitor for signs and symptoms of potential perforation, especially in subjects with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation.

Management of Immune-Related Hepatic Adverse Events

For guidelines for delaying a dose, refer to Section 6.2.1.2.3.	
Grade 1	Monitor LFTs as outlined in the protocol; **Worsening:** treat as Grade ≥2
Grade 2	Monitor every 3 days; **Returning to baseline:** resume per protocol monitoring **LFT elevation >5 days or worsening:** 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **LFT return to ≤Grade 1 or baseline:** taper steroids over at least 4 weeks; resume routine monitoring and resume study treatment per protocol
Grade 3-4	Monitor every ≤2 days; **Immediately:** 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist **Persistence >3 days or recurrence:** add mycophenolate mofetil 1g bid; if no response within ≤5 days consider other immunosuppressants per local guidelines **LFT return to Grade 2:** stop immunosuppressants **LFT return to ≤Grade 1:** taper steroids over at least 4 weeks

Management of Immune-Related Endocrinopathies

For guidelines for delaying a dose, refer to Section 6.2.1.2.3	
Asymptomatic TSH elevation	**TSH <0.5xLLN or TSH >2xULN or TSH >ULN in 2 subsequent measurements:** include free T4 assessment prior/after subsequent cycles of study treatment; consider endocrinology consultation
Symptomatic endocrinopathy	Assess endocrine function with appropriate laboratory testing; consider pituitary MRI scan **With abnormal lab and pituitary scan:** 1.0–2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics • In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard-of-care. **Clinical and laboratory improvement:** taper steroids over at least 4 weeks; patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component **Without abnormal lab and pituitary scan but symptoms persist:** repeat laboratory assessments in ≤3 weeks and MRI in 4 weeks
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Rule out sepsis **Immediately:** initiate/stress dose of IV steroids with mineralocorticoid activity; fluids IV; consult endocrinologist **Adrenal crisis ruled out:** treat as symptomatic endocrinopathy
Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	For T1DM or Grade 3-4 Hyperglycemia: Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered.

Management of Rash

For guidelines for delaying a dose, refer to Section 6.2.1.2.3.	
Grade 1-2	**Immediately:** Symptomatic therapy (eg, antihistamines, topical steroids) **Persistence ≤2 weeks or recurrence:** consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks **Worsening to >Grade 2:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤ Grade 1:** taper steroids over at least 4 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Management of Renal Adverse Events

For guidelines for delaying a dose, refer to Section 6.2.1.2.3.	
Grade 1	Monitor creatinine weekly **Creatinine returns to baseline:** continue monitoring per protocol **Creatinine increases:** treat as Grade ≥2
Grade 2-3	Monitor creatinine every ≤3 days **Immediately:** start 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics; consider renal biopsy **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks **Persistence >7 days or worsening:** treat as Grade 4
Grade 4	Monitor creatinine daily **Immediately:** consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Management of Neurological Adverse Events

For guidelines for delaying a dose, refer to Section 6.2.1.2.3	
Grade 1	Monitor per protocol **Worsening:** treat as ≥Grade 2
Grade 2	**Immediately:** treat symptoms according to institutional standards; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent **Worsening:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult neurologist; treat symptoms according to institutional standards; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics **Worsening or atypical presentation:** consider immunoglobulins IV (IVIG) or other immunosuppressive therapies according to institutional standards **Improvement to ≤ Grade 2:** taper steroids over at least 4 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Management of Pulmonary Adverse Events

For guidelines for delaying a dose, refer to Section 6.2.1.2.3.	
Grade 1	Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; re-image every 3 weeks **Worsening:** treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1-3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider hospitalization **Immediately:** start 1.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics **Persistence for 2 weeks or worsening:** treat as Grade 3-4 **Improvement to ≤ Grade 1 or baseline:** taper steroids over at least 4 weeks
Grade 3-4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy **Immediately:** 2-4 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; **Persistence for 2 days or worsening:** add immunosuppression (eg, infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) **Improvement to ≤ Grade 2:** taper steroids over at least 6 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids need to be considered

Management of Uveitis and Visual Complaints

For guidelines for delaying a dose, refer to Section 6.2.1.2.3.	
Grade 1	Thorough eye examination Topical corticosteroids should be considered Persisting despite topical steroids, treat as Grade 3-4
Grade 2	
Grade 3-4	Thorough eye examination Systemic corticosteroids

Amylase/Lipase Elevations

The recommended management of anti-PD-1 therapy-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low-grade levels over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly.

Attachment 2: 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 3: Anticipated Events

Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-specific events), or background regimen (androgen deprivation therapy [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 AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 12.3.2. 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) as per applicable clinical trial legislation to Health Authorities and IRB/IECs. 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/IECs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

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 by arm.

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 4: Additional Information on CYP450 Drug Interactions

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm[12]

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Attachment 5: Modified Schedule of Events for Combinations Closed to Enrollment

This attachment outlines instructions for continuation of treatment and required follow-up for the remaining subjects in combinations closed to enrollment.

When a combination is closed under an amendment, subjects who had signed the informed consent form prior to the approval date of the amendment will be allowed to complete screening and be enrolled if all inclusion/exclusion criteria for the combination (Sections 4.1, 4.2, and 4.3) are met.

Subjects already enrolled in a closed combination can continue to receive study medication until documented disease progression or the subject discontinues the study treatment for any reason as described in this attachment.

Under Attachment 5, limited data, including safety assessments will be collected. Other prostate cancer-related assessments will be per local practice, at the investigator's discretion.

Treatment Phase

Enrolled subjects must sign an updated informed consent form to continue in the study under an amendment. Subjects may continue to receive study medication as long as (in the opinion of the investigator) the subject is receiving benefit and not experiencing unacceptable toxicity; or until such time that the subject needs to start other anti-cancer treatment, withdraws consent, or is discontinued due to decision by the investigator or subject.

During the Treatment Phase, the subject will continue to receive treatment according to the dosing regimen outlined in Section 6, Dosage and Administration. An interactive web response system will be used to manage drug supply; study medication will be shipped directly to the site. The subject will be provided with a sufficient supply of oral study drug until the next planned visit, and drug accountability will occur at each site visit. Cycle numbering will continue from the last cycle the subject completed prior to switching to the modified schedule (ie, Cycle "X"). The first cycle under the amendment will be Cycle "X+1".

Subjects enrolled in Combination 1 will receive cetrelimab in the clinic. Before each IV administration of cetrelimab and oral dose of niraparib, mandatory laboratory tests (hematology and blood chemistry) and general physical status must be reviewed. Please follow instructions in Section 6.2.1.2.1, of the protocol for cetrelimab retreatment criteria.

Attachment 5: Modified Schedule of Events for Combinations Closed to Enrollment

Study Drug Preparation and Dispensing Instructions

Study drug administration and dosing compliance should be assessed at each site visit. A count of all oral study drug provided by the sponsor will be conducted in the Treatment Phase.

The study site must maintain accurate drug accountability records including dates and amount of study drug received, to whom dispensed, and accounts of any study drug accidentally or deliberately destroyed. Reconciliation must be made between the amount of study drug supplied,

dispensed, and subsequently destroyed or returned to sponsor or its representative. See Section 14.5, for instructions on drug accountability.

Dose modifications and Management of Toxicity

Please follow instructions in Sections 6.2.1, and 6.2.2, of the protocol.

For prohibited and restricted concomitant therapies, follow Sections 8.1, and 8.2, respectively of the protocol.

Study Evaluations to be Performed

Study evaluations will be performed according to the combination-specific Modified Schedule of Events below. Any additional assessments not specified in the Modified Schedule of Events can be performed at the discretion of the investigator according to routine practice.

Information regarding serious adverse events (as defined in Section 12.3.2) will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax). An End-of-Treatment Visit or phone call for a safety assessment should take place within 30 days after the last dose of study medication is administered.

Efficacy Evaluations to be Performed
Investigators should monitor and assess the subject for response to treatment or disease progression according to routine practice. (Refer to the Modified Schedule of Events below for efficacy evaluations.)

Safety Evaluations to be Performed
Safety assessments as outlined in the Modified Schedule of Events provided in this attachment will be performed while continuing treatment and for up to 100 days for subjects in Combination 1 and up to 30 days for subjects in Combination 2 after the last dose of study medication or until the start of subsequent systemic anticancer therapy. Any serious adverse event occurring during the study must be reported to the sponsor by investigational staff within 24 hours of their knowledge of the event.

Biomarker samples
No further samples, including archival formalin-fixed paraffin-embedded tumor samples, will be collected.

Attachment 5: Modified Schedule of Events for Combinations Closed to Enrollment

End-of-Treatment Visit

The End-of-treatment visit should occur within 30 days after administration of the last dose of study medication.

Subject Completion

The subject is considered to have completed the Treatment phase of the study after discontinuing treatment for any reason and having had a safety assessment at the End-of-treatment Visit or the subject is lost to follow-up.

The subject's study treatment will be discontinued if:

- The investigator or sponsor believes (eg, for safety or tolerability reasons such as an adverse event) that it is in the best interest of the subject to stop treatment
- The investigator believes the subject is no longer receiving clinical benefit from continued treatment
- The sponsor terminates the study

Subjects who discontinue the study drugs should complete the EoT visit within 30 days of the last dose of study drug or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. For subjects enrolled in Combination 1, another safety assessment via scheduled visit or phone call should take place within 100 to 114 days after the last dose of study medication is administered.

Subject Withdrawal From the Study

The subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Investigator’s decision

Source Documentation

At a minimum, the type and level of detail of source data available for the study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. This should also include: subject identification and study identification; study discussion and date of updated informed consent; dates of visits; serious adverse event information; drug dispensing/ return records (ie, bottle numbers) and study drug administration information. (See Section 17.4)

Attachment 5: Modified Schedule of Events for Combinations Closed to Enrollment

Modified Schedule of Events for Combination 1

	Treatment Phase		End of Treatment Phase	Visit or Phone Call	Follow-up Phase
CYCLE (treatment cycle is defined as 28 days)	**Amendment 6 Cycle X+1[1]**	**Every Cycle Until Treatment Discontinuation**	**End-of-Treatment Visit[2]**	**Day 100-114 after the last dose of study medication[2]**	**Every 3 Months**
Informed consent[3]	X				
Physical examination, including body weight	X	X	X		
Vital signs (blood pressure, temperature, heart rate)[4]	X	X	X		
Dispense oral study drug	X	X[5]			
Cetrelimab- IV Q4W (CxD1+7)[6]	X	X			
Drug accountability	X	X[5]	X		
Adverse events and serious adverse events[7]	X	X	X	X	
Hematology (central or local)[8]	X	X			
Blood chemistry (central or local)[8]	X	X			
CT or MRI; Bone scan (^{99m}Tc)	*At the discretion of the investigator according to routine practice.*				
Survival status and subsequent therapies[9]	*Collected continuously from signing the ICF until the end of study (including during the Follow up Phase)*				

CT=computed tomography; ICF=informed consent form; MRI=magnetic resonance imaging; ^{99m}Tc=technetium-99m.

1 Cycle "X+1" will be the first cycle under Amendment 6. Cycle "X" is the last cycle the subject completed prior to switching to the modified schedule.

2 EoT Visit: The EoT visit for a safety assessment must be scheduled within 30 days after both study drugs are discontinued, or prior to administration of a new anti prostate cancer therapy, whichever occurs first. Another safety assessment via scheduled visit or phone call should take place within 100 to 114 days after the last dose of study medication is administered.

3 Subjects who have signed the informed consent form prior to implementation of Amendment 6 will be allowed to complete screening and be enrolled if all inclusion/exclusion criteria are met. For those subjects who are currently enrolled in Combination 1, the investigator is to confirm that the subject is receiving benefit from the study drug in order to continue on study.

4 Blood pressure should be assessed weekly during the first 2 months of treatment (Cycles 1 and 2), then monthly from Cycle 3 onward. Follow instructions in Section 6.1.1, for vital sign assessments during cetrelimab infusion.

5 The subject will be provided with a sufficient supply of oral study drug until the next planned visit. Drug accountability will occur at each site visit.

6 For cetrelimab retreatment criteria and instructions for dose delay refer to Section 6.2.1.2.

7 See Section 12.3.1, and 12.3.2, for instructions on reporting adverse events and serious adverse events.

8 Hematology: Complete blood count should be performed weekly during the first month of treatment (Cycle 1). Blood chemistry tests to be performed are fasting glucose, AST, ALT and bilirubin. Liver function tests should be performed every other week during the first 3 months of treatment (Cycles 1 through 3). See Section 6, of the protocol for retreatment criteria for cetrelimab, dose modification, and management of toxicity for study medications.

9 Study data for survival and subsequent therapies will continue to be collected after discontinuation of treatment, unless the subject withdraws consent for further study participation.

Attachment 5: Modified Schedule of Events for Combinations Closed to Enrollment

Modified Schedule of Events for Combination 2

	Treatment Phase		End of Treatment Phase	Follow-up Phase
CYCLE (treatment cycle is defined as 28 days)	**Amendment 4 Cycle X+1[1]**	**Every Cycle Through Cycle 12; Cycle 13 and Beyond, Every 2 Cycles Until Treatment Discontinuation[2]**	**End-of-Treatment Visit (within 30 days of last dose)[3]**	**Every 3 months**
Visit Window		(±3 days)	(±5 days)	(±2 weeks)
Study Procedures[4]				
Informed consent[5]	X			
Dispense study drug	X	X[6]		
Drug accountability	X	X[6]	X	
Serious Adverse Events[7]	X	X	X	
CT or MRI; Bone scan (^{99m}Tc)	*At the discretion of the investigator according to routine practice.*			
Clinical safety laboratory tests (central or local)	*At the discretion of the investigator according to routine practice and per local label for abiraterone acetate.*			
Blood pressure	*Every 2 cycles.*			
Serum PSA	*At the discretion of the investigator according to routine practice.*			
Survival Status and subsequent therapies[8]	*Collected continuously from signing the ICF until the end of study (including during the Follow up Phase)*			

CT=computed tomography; EoT=End of Treatment; ICF=informed consent form; MRI=magnetic resonance imaging; PSA=prostate-specific antigen; ^{99m}Tc=technetium-99m.

1 Cycle "X+1" will be the first cycle under Amendment 4. Cycle "X" is the last cycle the subject completed prior to switching to the modified schedule.

2 Study visits may have a ±4-day window.

3 EoT Visit: The EoT visit for a safety assessment must be scheduled within 30 days after both study drugs are discontinued, or prior to administration of a new anti-prostate cancer therapy, whichever occurs first.

4 Response and safety evaluations (other than serious adverse event reporting) are to be performed at the discretion of the investigator according to routine practice.

5 Only subjects who have signed the informed consent form prior to the Internal Review Board/Internal Ethical Committee approval date of Amendment 4 will be allowed to complete screening and be enrolled if all inclusion/exclusion criteria for Combination 2 are met. For those subjects who are currently enrolled in Combination 2, the investigator is to confirm that the subject is receiving benefit from the study drug in order to continue on study.

6 The subject will be provided with a sufficient supply of study drug until the next scheduled visit. Drug accountability will occur at each site visit.

7 See Section 12.3.1, and 12.3.2, of the protocol for instructions on reporting adverse events and serious adverse events.

8 Study data for survival and subsequent therapies will continue to be collected after discontinuation of treatment, unless the subject withdraws consent for further study participation.

Attachment 6: Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination

This Attachment outlines the design and procedures associated with Combination 3. Cross references back to the protocol are included as appropriate.

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TIME AND EVENTS SCHEDULE 1A: STUDY PROCEDURES AND ASSESSMENTS FOR COMBINATION 3 (NIRAPARIB/ABIRATERONE ACETATE FIXED DOSE COMBINATION)

Phase	Screening	PK Assessment Phase		Extension Phase								End of Treatment Visit
	≤21 days before first dose	Study Days 1 8[a]		Cycle 1, Day 1 (Study Day 8)[a] until study treatment discontinuation								within 30 days after the last dose of study medication[b]
Cycle (defined as 28 days)				**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycles 4 to 12 (Every Cycle)**	**Cycle 13 Onward (Every Other Cycle)**	
Cycle Day				**1**	**15**	**1**	**15**	**1**	**15**	**1**	**1**	
Study Day		**1**	**2-8**									
Visit Window				**+4 days**	**±4 days**							**±7 days**
Informed Consent[c]	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Medical History	X											
Physical Examination[d]	X	X[e]	*As per routine practice*									
Vital Signs (blood pressure[f], temperature, heart rate, height, weight)	X	X[e]	*Blood pressure should be measured weekly during Cycles 1 & 2, and then monthly thereafter. Other vital signs are per routine practice*									
ECOG PS	X	X[e]										
Prior Prostate Cancer Treatment	X											
Concomitant medications	X	X	X									
Electrocardiogram (12 lead)	X											
Recommended biomarker panel for HRR gene alteration status determination[k]	X											
Screening Laboratory Tests (central)[g]	X											
Clinical Safety Laboratory Tests (central or local)[h]				**X (weekly)**		**X**	**X**	**X**	**X**	*As per routine practice*		
Dispense Study Medication		**X**		**X[i]**		**X[i]**		**X[i]**		**X[i]**	**X[i]**	
Drug Accountability & Treatment Compliance		**X**		**X**		**X**		**X**		**X**	**X**	
Pharmacokinetic Assessments		*See PK T&E Schedule 1B*										
Adverse Events[j]	*Continuous from signing the ICF through the PK Assessment Phase[a]*											
Serious Adverse Events[j]	*Continuous from signing the ICF through End of Treatment Visit*											

Phase	Screening	PK Assessment Phase		Extension Phase								End of Treatment Visit
	≤21 days before first dose	Study Days 1 8[a]		Cycle 1, Day 1 (Study Day 8)[a] until study treatment discontinuation								within 30 days after the last dose of study medication[b]
Cycle (defined as 28 days)				**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycles 4 to 12 (Every Cycle)**	**Cycle 13 Onward (Every Other Cycle)**	
Cycle Day				**1**	**15**	**1**	**15**	**1**	**15**	**1**	**1**	
Study Day		**1**	**2-8**									
Visit Window				**+4 days**	**±4 days**							**±7 days**

AE adverse event; ECOG PS Eastern Cooperative Oncology Group Performance Status; HRR homologous recombination repair; PK pharmacokinetic; SAE serious adverse event; T&E Time and Events Schedule

[a] Cycle 1 Day 1 of the Extension Phase starts after the 168-hour PK sampling on Day 8.

[b] The End of Treatment Visit must be scheduled within 30 days after both study drugs are discontinued, or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. This visit may take place as a clinic visit or phone call at the discretion of the investigator.

[c] Must be signed before first study-related procedure.

[d] At screening, a full physical examination should be performed. Thereafter, limited symptom-directed physical examinations may be performed. Only clinically relevant abnormalities should be recorded as AEs/SAEs in the electronic CRF.

[e] Screening results may be used if performed within 14 days before Day 1.

[f] Blood pressure monitoring can occur at clinic visit or may also be reported to the site by the subject, by home nurse, or by other method deemed reliable by the investigator.

[g] Screening laboratory assessments (see Table 2) must be performed centrally.

[h] Clinical safety laboratory tests (see Table 3) can be performed centrally or locally. Complete blood cell counts should be performed according to local label for niraparib: weekly during Cycle 1, monthly during Cycles 2-12, and then periodically after this time. Liver function tests should be performed according to local label for abiraterone acetate every 2 weeks (eg, on Day 1 and 15) during Cycles 1-3, and then monthly thereafter.

[i] Subjects will be given a 1-month supply of study drug at each visit up to Cycle 12, and then a 2-month supply from Cycle 13 onward.

[j] See Protocol Sections 12.3.1, and 12.3.2, for instructions on reporting AEs and SAEs.

[k] HRR gene alteration status assessment by the sponsor from tissue samples (archival) is recommended but not required for trial eligibility. Subjects already receiving study treatment may have samples submitted after reconsent.

TIME AND EVENTS SCHEDULE 1B: PHARMACOKINETIC ASSESSMENTS FOR COMBINATION 3 (NIRAPARIB/ABIRATERONE ACETATE FIXED DOSE COMBINATION)

	Pharmacokinetic Assessment Phase				
Study Day	**Time**	**Study Drug Administration[a]**	**PK blood sample**	**PK sampling window**	**Meal[b]**
Day 1	**Predose**		X		
	0	X			
	30 min		X	±3 min	
	1 hour		X	±6 min	X[c]
	1 hour 30 min		X	±9 min	
	2 hours		X	±12 min	
	3 hours		X	±18 min	
	4 hours		X	±24 min	X[d]
	6 hours		X	±30 min	
	8 hours		X	±30 min	X[e]
	10 hours		X	±30 min	
Day 2	24 hours		X	±30 min	
Day 3	48 hours		X	±30 min	
Day 4	72 hours		X	±1 hr	
Day 8[f]	168 hours		X	±1 hr	

AA=abiraterone acetate; FDC=fixed-dose combination; min=minutes; PK=pharmacokinetic; SA=single agent

[a] Niraparib + AA either as FDC or as SA. Niraparib and AA will be administered together in the morning.
[b] Separate instructions will be provided.
[c] A low-fat breakfast will be given 1 hour after dosing. Consumption is allowed for 30 minutes.
[d] Lunch to be given after collection of the 4-hour PK blood sample. Consumption is allowed for 1 hour.
[e] The dinner/evening meal should be consumed between 4 and 8 hours after lunch. A light snack may be consumed between lunch and dinner.
[f] Cycle 1 Day 1 of the Extension Phase starts after the 168-hour PK sampling on Day 8.

Note: PK samples should be taken as close to the nominal time as possible.

1. INTRODUCTION

See the Protocol Introduction for an overall summary of Background Design Rationale (Section 1.1), Available Nonclinical and Clinical Data for Niraparib (Section 1.2), Summary of Available Nonclinical and Clinical Data for Combination Agents (Section 1.3), and Benefit/Risk Assessment (Section 1.4).

For this ongoing Combination, the terminology for biomarkers has been revised; "DRD and CDK12 pathogenic alterations" have been replaced with "homologous recombination repair (HRR) gene alterations" to indicate the inclusion of alterations outside of the DNA-repair pathway (eg, CDK12).

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the relative bioavailability of 2 regular-strength FDC tablet formulations of niraparib and AA with respect to niraparib and AA co-administered as SA under fasted conditions in subjects with mCRPC	• PK parameters (C_{max}, $[C_{max}/dose]_{niraparib}$, $AUC_{0\text{-}168h}$, $[AUC_{0\text{-}168h}/dose]_{niraparib}$) of niraparib and AA after a single dose
Secondary	
• To evaluate the PK of a low-strength FDC tablet formulations of niraparib and AA under fasted conditions in subjects with mCRPC • To assess the safety of niraparib in combination with AA in subjects with mCRPC	• PK parameters (C_{max}, $[C_{max}/dose]_{niraparib}$, $AUC_{0\text{-}168h}$, $[AUC_{0\text{-}168h}/dose]_{niraparib}$) of niraparib and AA after a single dose • Adverse events and clinical laboratory safety
AA=abiraterone acetate; $AUC_{0\text{-}168h}$=area under the plasma concentration versus time curve over 7 days; C_{max}= maximum observed plasma concentration after a single dose; FDC=fixed-dose combination; mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetic; SA=single agent	

2.2. Hypothesis

Combination 3 is an estimation study to assess the relative BA of niraparib and AA as FDC tablet formulations compared to SA under fasted conditions by providing the point estimate and associated precisions of the geometric mean ratios (GMRs) between the FDC test formulations and the SA reference formulation for the primary PK parameters. No formal hypothesis will be tested.

3. STUDY DESIGN

3.1. Overview of Study Design

See Protocol Section 3.1, for general information regarding the end-of-study and end-of-combination definitions, as well as information related to clinical study reports, data cutoff dates, and monitoring of subjects who continue to receive study drug(s) after the data cutoff.

Combination 3 is an open-label, multi-center, partly randomized (Cohort 1 only), parallel group study to determine the PK and safety of 2 FDC tablet formulations of niraparib+AA in men with

mCRPC. The study will consist of a 21-day Screening Phase to determine eligibility, an open-label PK Assessment Phase of 8 days (Study Days 1-8, inclusive), followed by an Extension Phase during which treatment will be continued from Cycle 1 Day 1 (Study Day 8) until discontinuation. Subjects are recommended to submit tissue for identification of HRR gene alterations. Subjects testing positive for an HRR gene alteration will be advised to continue treatment with niraparib and AAP. Subjects testing negative for HRR gene alterations or for whom HRR gene alteration status is unknown will be allowed to continue treatment with niraparib and AAP or AAP alone at the investigator's discretion. Treatment will be continued from Cycle 1 Day 1 (Study Day 8) until discontinuation.

During the PK Assessment Phase, 3 cohorts will be studied. The Study Design is presented in Table 1 below.

- Cohort 1: subjects (N 34) will be randomized to receive a single dose of niraparib plus AA (200 mg niraparib + 1,000 mg AA) given as FDC1 regular-strength tablet formulation (G010) (Treatment Arm B [Cohort 1B], N 17) or as SAs (Treatment Arm A [Cohort 1A], N 17). Relative BA of the FDC1 regular-strength tablet will be assessed by comparing PK results from Cohort 1A to Cohort 1B.
- Cohort 2: subjects (N 17) will be assigned to receive a single dose of niraparib plus AA (200 mg niraparib + 1,000 mg AA) as FDC2 regular-strength tablet formulation (G012) (Treatment Arm C, Cohort 2C). Relative BA of the FDC2 regular-strength tablet will be assessed by comparing the PK results from Cohort 2C to Cohort 1A.
- Cohort 3: subjects (N 17) will be assigned to receive a single dose of niraparib plus AA (100 mg niraparib + 1,000 mg AA) as a low-strength FDC1 (G009) (Treatment Arm D [Cohort 3D]) or FDC2 (G014) (Treatment Arm E [Cohort 3E]) tablet formulation. The selection of Cohort 3D or 3E will be based on the relative BA results from Cohorts 1 and 2. Relative BA of the FDC1 or FDC2 low-strength tablet formulation will be assessed by comparing the PK results from Cohort 3D or 3E, respectively, to Cohort 1A.

In total, approximately 68 subjects will be enrolled. Approximately 34 subjects with mCRPC are planned to be enrolled in Cohort 1 and approximately 17 subjects with mCRPC are planned to be enrolled in each of Cohorts 2 and 3.

Subjects will be randomly assigned to 1 of 2 treatment arms in Cohort 1 which include Treatments A and B as shown in Table 1. Subjects will be assigned to Treatment C in Cohort 2 and Treatment D or E in Cohort 3 (based on the interim analysis results for Cohort 1).

Table 1: Study Cohorts and Treatments

			PK Assessment Phase (fasting)[a]	Extension Phase[b] (modified fasting)[c]
Cohort	**Treatment Arm**	**No. of Subjects**	**Study Days 1-8**	**(C1D1 until EOT) C1D1= Study Day 8 after 168-hr PK sample**
1	A	17	Single Dose 200 mg niraparib/1,000 mg AA as SA	niraparib 200 mg QD AA 1,000 mg QD prednisone 5 mg BID as SA or AA 1,000 mg QD prednisone 5 mg BID as SA[d]
	B	17	Single Dose 200 mg niraparib/1,000 mg AA as FDC1 regular-strength tablets (G010)	
2	C	17	Single Dose 200 mg niraparib/1,000 mg AA as FDC2 regular-strength tablets (G012)	
3	D or E	17	Single Dose 100 mg niraparib/1,000 mg AA as FDC1 (G009) or FDC2 (G014) low-strength tablets	

Treatments A and B will be randomized; whereas subjects will be assigned to Treatment C and D or E
AA=abiraterone acetate; BID=twice daily; EOT=end of treatment; FDC=fixed-dose combination; QD=once daily; SA=single agent
Treatment A: 2 x 100 mg capsules niraparib plus 4 X 250 mg tablets AA current commercial formulation
Treatment B: 2 x FDC1 regular-strength tablets (100 mg niraparib/500 mg AA)
Treatment C: 2 x FDC2 regular-strength tablets (100 mg niraparib/500 mg AA)
Treatments D or E: 2 x FDC1 or FDC2 low-strength tablets (50 mg niraparib/500 mg AA)

[a] Subjects must fast from food and fluids (excluding noncarbonated water) for at least 10 hours before dosing. Intake of water is allowed until 2 hours before study drug intake.
[b] Subjects continue treatment until disease progression, withdrawal of consent, loss to follow-up, lack of clinical benefit in the opinion of the investigator, or sponsor ends the study.
[c] Modified fasting defined as study drug intake on empty stomach only: intake at least 1 hour before or at least 2 hours after a meal.
[d] Subjects will receive niraparib + AA or AA alone QD, each in combination with 5 mg prednisone (or prednisolone) BID, during the Extension Phase at the investigator's discretion guided by HRR gene alteration status.

Enrollment will start in Cohort 1 first. Subjects will be randomized 1:1 to Cohort 1B and Cohort 1A in a parallel group design. Pharmacokinetic sampling will be performed up to 168 hours post-dose on Study Day 8 (Cycle 1 Day 1). An interim PK analysis will be conducted after 8 PK evaluable subjects from each treatment group (N 16) complete PK assessments over 168 hours. Results from the interim analysis will determine the initiation of Cohort 2 and Cohort 3. Enrollment will continue during the interim PK analysis.

All subjects in Cohort 2 and Cohort 3 will follow the same PK assessments as described for Cohort 1 in the above paragraph.

Cohort 2 will test FDC 2 regular strength (G012).

Cohort 3 will test the low strength of 1 of the FDC tablet formulations (FDC 1 [G009] or FDC2 [G014]).

Combination 3 procedures and timepoints are summarized in Time and Events Schedule 1A; PK assessments are summarized in Time and Events Schedule 1B.

Biomarker status is not required to determine study eligibility. If not already known, biomarker status assessment is recommended, and results can be used to guide further treatment decisions during the Extension Phase.

Based on the results of the interim analysis from the MAGNITUDE Study (see Section 1.1.3), the IDMC determined that the futility rule was met, indicating the study did not show additional benefit of adding niraparib to AAP in subjects with no HRR gene alterations. No new safety signals were identified.

After completion of the PK Assessment Phase, subjects will enter the Extension Phase to receive treatment with either niraparib 200 mg once daily plus AA 1,000 mg once daily (both as SAs) and prednisone/prednisolone 5 mg twice daily or AA 1,000 mg once daily and prednisone/prednisolone 5 mg twice daily; treatment cycles are 28 days. Subjects testing positive for HRR gene alterations will be advised to continue treatment with niraparib and AAP. Subjects testing negative for HRR gene alterations or for whom HRR gene alteration status is unknown will be allowed to continue treatment with niraparib and AAP or AAP alone at the investigator's discretion.

Study evaluations during Extension Phase will be performed according to Time and Events Schedule 1A. Any additional assessment not specified in this table can be performed at the discretion of the investigator according to routine practice. Treatment will continue until discontinuation for disease progression, unacceptable toxicity, withdrawal of consent, loss to follow up, lack of clinical benefit in the opinion of the investigator, start of subsequent anticancer therapy, or the Sponsor ends the study (see Protocol Section 10).

In the event of early study completion or study termination by the sponsor, (whether or not the study endpoints are met), the sponsor will continue to provide study treatments until unequivocal disease progression, unacceptable toxicity, or an alternate method is in place to avoid treatment interruption.

3.2. Dose Selection Rationale

The RP2D of niraparib in combination with AAP is 200 mg based on Study 64091742PCR1001 (See Protocol Section 3.2.2).

3.3. Safety Evaluation Criteria

Safety evaluations will be performed as outlined in Time and Events Schedule 1A.

4. SUBJECT POPULATION

Investigators should ensure that all enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that he no longer meets all eligibility criteria, then the subject should be excluded from participation. Retesting of values (eg, safety laboratory assessments) that lead to exclusion will be allowed once using an unscheduled visit during the Screening Phase to reassess eligibility.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Combination 3.

1. Male

2. >18 years of age (or higher legal age of consent in the jurisdiction in which the study is taking place).

3. Signed informed consent form (ICF) indicating that he understands the purpose of, and procedures required for, the study and is willing to participate in the study.

4. Histologically or cytologically confirmed prostate cancer.

5. Diagnosed with mCRPC, who in the opinion of the investigator may benefit from treatment in Combination 3 of this study.

6. Able to continue GnRHa therapy during the study if not surgically castrate (ie, subjects who has not undergone bilateral orchiectomy).

7. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤1.

8. Toxicity associated with prior chemotherapy or radiotherapy has resolved to Grade ≤1 (except alopecia or Grade ≤2 neuropathy) at screening.

9. Criterion modified per Amendment 6

   9.1 While on study medication and for 3 months following the last dose of study medication, a male subject must agree to use an adequate contraception method as deemed appropriate by the investigator and as specified in Section 4.3. Prohibitions and Restrictions

10. Subject must agree not to donate sperm while on study treatment, and for 3 months following the last dose of study treatment.

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

a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L independent of growth factors for 30 days

b. Hemoglobin ≥9.0 g/dL independent of transfusion for 30 days

c. Platelet count ≥100 x 10^9/L independent of growth factors or transfusion for 30 days

d. Serum albumin ≥3.0 g/dL

e. Serum creatinine ≤1.5 × the upper limit of normal (ULN), or a calculated creatinine clearance ≥30 mL/min/1.73 m^2 using the MDRD or CKD-EPI equation

f. 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 × ULN, measure direct and indirect bilirubin, and if direct bilirubin is ≤1.5 × ULN, subject may be eligible)

g. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤3 x ULN

h. Fasting glucose ≤ 250 mg/dL

12. Subject must be willing and able to adhere to the prohibitions and restrictions specified in Section 4.3.

13. Subject must be able to swallow the study drug tablet or capsule whole.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Combination 3.

1. Symptomatic brain metastases.

2. Prior disease progression during combination treatment with AA and PARPi. Prior discontinuation of treatment with AA or PARPi due to AA- or PARPi-related toxicity.

3. History or current diagnosis of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).

4. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

   a. non-muscle invasive bladder cancer.

   b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.

   c. Breast cancer:

      adequately treated lobular carcinoma in situ or ductal carcinoma in situ,

      or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.

   d. Malignancy that is considered cured with minimal risk of recurrence

5. Known allergies, hypersensitivity, or intolerance to niraparib or AA or the corresponding excipients of niraparib/AA.

6. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

7. Known disorder affecting gastrointestinal absorption. The eligibility of subjects with prior gastrointestinal surgery, which may affect gastrointestinal absorption (eg, partial gastrectomy and small/large bowel resection) should be discussed with the sponsor's medical monitor.

8. Severe or unstable angina, myocardial infarction or ischemia requiring coronary artery bypass graft or stent within the previous 6 months, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to randomization or New York Heart Association (NYHA) Class II to IV heart disease.

9. Presence of uncontrolled hypertension (systolic blood pressure [BP] ≥ 160 mmHg or diastolic BP ≥ 100 mmHg). Subjects with a history of hypertension are allowed provided that BP is controlled to within these limits (systolic BP < 160 mmHg and diastolic BP < 100 mm Hg) by anti-hypertensive treatment.

10. Subjects with lack of safe and reliable peripheral intravenous access.

11. History of adrenal dysfunction.

12. Human immunodeficiency virus (HIV)-positive patients 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 13.c, a change is made to avoid a potential drug-drug interaction with the study drug)
    c. Receiving antiretroviral therapy that may interfere with study treatment (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

13. Prior antitumor therapy as follows, before the first dose of study drug (Study Day 1):
    a. anti-androgen therapy: abiraterone acetate within 2 weeks, enzalutamide within 8 weeks, apalutamide within 6 weeks, other anti-androgens (eg, bicalutamide, flutamide, nilutamide) within 2 weeks, and PARPi (eg. olaparib, niraparib, rucaparib) within 2 weeks
    b. chemotherapy or immunotherapy for treatment of prostate cancer within 28 days
    c. investigational agent for treatment of prostate cancer within 28 days.
14. If a subject has undergone major surgery, they must have recovered adequately from the toxicities or complications from the intervention prior to starting therapy.
15. Active hepatitis B virus (eg. Hepatitis b surface antigen reactive) or hepatitis C virus (HCV) (eg. HCV RNA quantitative is detected) or chronic liver disease (as evidenced by ascites or bleeding disorders secondary to hepatic dysfunction).

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the study to be eligible for participation:

1. Must agree to always use a condom during sexual intercourse (even in case of prior vasectomy or in case of intercourse with an already pregnant woman) or remain abstinent during the study and for 3 months after the last study treatment administration (Section 10.2, Discontinuation of Study Treatment).

   If the patient is engaged in sexual activity with a woman of childbearing potential, then a condom should be used along with another highly effective contraceptive method. Highly effective methods of contraception (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

   combined hormonal (estrogen + progesterone or progesterone only) contraception associated with inhibition of ovulation: oral, injectable or implantable;

   placement of an intrauterine device (IUD) or intrauterine hormone releasing system (IUS);

   bilateral tubal occlusion;

   vasectomy;

   sexual abstinence; please note that sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

   A highly effective contraceptive method should be used for the duration of the study and for 3 months after the last study medication administration.
2. May not consume food or beverages containing grapefruit, Seville oranges, or quinine from 24 hours (72 hours in the case of grapefruit and Seville oranges) before each intensive PK sample collection day until after the last PK sample is collected in relation to the specific PK sampling period.

3. May not consume alcohol from 24 hours before each intensive PK sample collection day until after the last PK sample is collected in relation to the specific PK sampling period. Moderate (limited) alcohol consumption is allowed on other study days.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Randomization

Randomization will be used in Cohort 1 between Treatment Arms A and B only to avoid bias in the assignment of subjects to treatment sequence groups, to increase the likelihood that known and unknown patient attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment sequence groups, and to enhance the validity of statistical comparisons across the groups.

Approximately 34 subjects (17 subjects per arm) will be enrolled into Cohort 1 of the study (2 parallel treatment arms). As subjects qualify for the study, they will be assigned a subject randomization number in strict sequential order. Based on a computer-generated randomization schedule prepared under the sponsor's supervision before the start of the study, subjects will be randomly assigned to receive the treatments in 1 of 2 possible treatment groups (A, B). Assignment to treatment group will occur before a subject receives the study drug.

Subjects who drop out during the PK assessment phase may be replaced to assure at least 30 subjects complete Cohort 1. Subjects who are replaced during the PK Assessment Phase may continue to the Extension Phase.

Cohorts 2 and 3 are nonrandomized. Subjects will be assigned to Treatment C in Cohort 2 and Treatment D or E in Cohort 3.

5.2. Blinding

Blinding will not be used because the primary endpoint, the assessment of specified PK parameters, is not subject to bias from the subjects or observers.

6. DOSAGE AND ADMINISTRATION

An interactive web response system (IWRS) will be used to manage drug supply during both the PK Assessment and Extension Phases; study medication will be shipped directly to the site.

There are separate dosing and administration schedules for the PK and Extension Phases of Combination 3 (see Time and Events Schedule 1A and 1B).

6.1. Study Drug Administration

6.1.1. Pharmacokinetic Assessment Phase

During the PK Assessment phase (Day 1 through 8), all subjects will be assigned to one of the treatment arms below.

Study Treatment

Reference Treatment

- Treatment A (SA): 200 mg niraparib commercial formulation given as 2 X 100 mg capsules plus 1,000 mg AA current commercial formulation given as 4 X 250 mg tablets, administered orally under fasted conditions.

Test Treatments

- Treatment B (FDC1 regular-strength [G010]): 200 mg niraparib/1,000 mg AA given as 2 X FDC1 regular-strength (G010) tablets (100 mg niraparib/500 mg AA), administered orally under fasted conditions.
- Treatment C (FDC2 regular-strength [G012]): 200 mg niraparib/1,000 mg AA given as 2 X FDC2 regular-strength (G012) tablets (100 mg niraparib/500 mg AA), administered orally under fasted conditions.
- Treatment D (FDC1 low-strength [G009]): 100 mg niraparib/1,000 mg AA given as 2 X FDC1 low-strength (G009) tablets (50 mg niraparib/500 mg AA), administered orally under fasted conditions.
- Treatment E (FDC2 low-strength [G014]): 100 mg niraparib/1,000 mg AA given as 2 X FDC2 low-strength (G014) tablets (50 mg niraparib/500 mg AA), administered orally under fasted conditions.

Dosing Instructions

- Subjects must refrain from taking the study drugs on the mornings of study visits designated for PK sampling until seen at the site.
- On intensive PK sampling day (Study Day 1) in Cohorts 1-3:

  Subjects must fast from food and fluids (excluding noncarbonated water) for at least 10 hours before dosing. Intake of water is allowed until 2 hours before study drug intake.

  The study drugs will be administered orally shortly after the planned pre-dose PK sampling is completed with a total amount of 240 mL noncarbonated water. An additional 50 mL of noncarbonated water is allowed if necessary. Study treatment must be swallowed whole and not chewed, divided, dissolved, or crushed.

  Subjects will receive a low-fat breakfast exactly 1 hour after study drug administration and will continue fasting until 4 hours after study drug administration. The breakfast should be eaten completely within 30 minutes or less.

  The drinking of noncarbonated water is allowed from 1 hour after study drug administration onwards.

  Lunch will be served on intensive PK sampling day after collection of the 4-hour PK blood sample.

  Dinner/evening meal should be consumed between 4 and 8 hours after lunch. A light snack may be consumed between lunch and dinner.

  Subjects who vomit 2 times at or before 3 hours after dosing of study drugs will be non-evaluable for PK assessment and will be replaced. Subjects who vomit beyond

3 hours after dosing of study drugs can continue the PK assessments if the subject and investigator agree.

- On Study Day 8 (Cycle 1 Day 1) study drugs will be taken after the planned pre-dose PK sampling is completed.

6.1.2. Extension Phase

During the Extension Phase, subjects will receive either niraparib 200 mg once daily plus AA 1,000 mg once daily or AA 1,000 mg once daily (as SAs) under modified fasted conditions each with prednisone/prednisolone 5 mg twice daily; treatment cycles are 28 days. Treatment will be at the discretion of the investigator guided by HRR gene alteration status. See Protocol Section 6.1, and 6.1.2, for dosage and administration instructions.

6.2. Dose Modification and Management of Toxicity During Extension Phase

Refer to Protocol Section 6.2, Dose Modification and Management of Toxicity, and Section 6.2.3, Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet, for dose modification instructions.

7. TREATMENT COMPLIANCE

During the PK Assessment Phase, study treatment will be administered at the study site under the supervision of study-site personnel.

During the Extension Phase, study drug administration and dosing compliance should be assessed as described in Time and Events Schedule 1A. A count of all study drug provided by the sponsor should be conducted. See Protocol Sections 7, and 7.2, for further instructions regarding niraparib+AAP and AAP compliance during the Extension Phase of Combination 3.

8. PRIOR AND CONCOMITANT THERAPY

All prior therapy for prostate cancer must be collected. Concomitant therapies must be recorded beginning with the signing of the ICF to the end of the PK assessment phase. In addition, concomitant medications for drug-related SAEs that occur during the Extension Phase must be recorded up to 30 days after the last dose of study drugs.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a patient into the study. All subjects should maintain the same medications throughout the entire study period, as medically feasible, with minimum introduction of new chronic therapies up to the start of the Extension Phase (Study Day 8 [Cycle 1 Day 1]). All therapies different from the study treatment must be recorded in the eCRF.

Continuous treatment with a GnRHa, or surgical castration, is mandatory for all subjects. The choice of GnRHa is at the discretion of the investigator. Dose and dose schedule (without interruption) will be consistent with the prescribing information and should be adjusted, if clinically indicated, to maintain castrate concentrations of testosterone. Recorded information will

include a description of the type of the drug, treatment period, dosing regimen, route of administration, and indication.

See Exclusion Criteria 13 in Section 4.2, of this Attachment for prior anti-cancer therapy wash-out period.

8.1. Prohibited Concomitant Therapies

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

The following concomitant medications are prohibited during the duration of the study:

- Anticancer therapies other than the study drugs, excluding GnRHa
- Experimental agents other than the study drugs
- Strong CYP3A4 inducers (See Protocol Attachment 4)
- Prednisone >10 mg (or any other corticosteroid for systemic use) per day is prohibited during the PK assessment phase. Patients receiving prednisone ≤10 mg (or any other corticosteroid for systemic use) per day prior to enrollment can continue the same dose during the PK assessment phase

The following concomitant medications are prohibited within 4 weeks prior to and during the PK Assessment Phase up to the start of the Extension Phase.

- Inhibitors/inducers of P-glycoprotein (P-gp), gene ABCB1:

  inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil

  inducers: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, tipranavir/ritonavir

8.2. Restricted Concomitant Medications

Refer to Protocol Section 8.2, Restricted Concomitant Medications, and Section 8.2.2, Combination 2: Niraparib and AAP for instructions.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules 1A and 1B summarize the frequency and timing of PK and safety assessments applicable to Combination 3.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECGs, vital signs, and any type of blood draw last. Actual dates and times of assessments will be recorded in the source documentation.

For each subject, the planned maximum amount of blood drawn will not exceed 70 mL at any visit. Refer to the study 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. Screening Phase

During the Screening Phase, eligibility criteria will be reviewed and evaluations performed as specified in Time and Events Schedule 1A. Screening procedures may be performed within 21 days before Study Day 1, unless otherwise specified. The screening physical exam and clinical safety laboratory evaluations can be used for Study Day 1 assessments if performed within 14 days. Assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent form (ICF) has been obtained, provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to enrollment.

Subjects who do not meet all inclusion criteria, or who meet an exclusion criterion, may be rescreened once. Rescreening is at the discretion of the investigator and requires sponsor approval and agreement. 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 to determine eligibility if not the reason for the rescreening. All other rescreening and subsequent enrollment activities must be conducted in accordance with all protocol defined windows and timelines.

9.1.3. PK Assessment Phase

The PK assessment phase will begin on Study Day 1 and end on Study Day 8 after completion of the 168-hour PK sampling. An overview of procedures and timepoints is provided in Time and Events Schedules 1A and 1B. A description of PK evaluations is in Section 9.3, of this Amendment.

9.1.4. Extension Phase

The Extension Phase will start on Study Day 8 (Cycle 1 Day 1) after completion of the 168-hour PK sampling in the PK Assessment Phase. Subjects testing positive for HRR gene alterations will be advised to continue treatment with niraparib and AAP. Subjects testing negative for HRR gene alterations or for whom HRR gene alteration status is unknown will be allowed to continue treatment with niraparib and AAP or AAP alone at the investigator's discretion. Treatment during the Extension Phase will be administered as single agents: niraparib 200 mg once daily, AA 1,000 mg once daily, and prednisone/prednisolone 5 mg twice daily in 28-day cycles.

Study evaluations during the Extension Phase will be performed according to Time and Events Schedule 1A. Any additional assessments not specified in Time and Events Schedule 1A may be performed at the discretion of the investigator according to routine practice. Treatment will continue until discontinuation for disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, lack of clinical benefit in the opinion of the investigator, start of subsequent anticancer therapy, or the sponsor ends the study.

9.1.5. End-of-Treatment Visit

See Protocol Section 9.1.5, End-of-Treatment Visit. For Combination 3, this visit can take place as a scheduled visit or phone call at the discretion of the investigator.

9.2. Antitumor Activity

No antitumor assessments will be done for Combination 3.

9.3. Pharmacokinetic Evaluations

9.3.1. PK Sample Collection and Handling

Venous blood samples will be collected for determination of plasma concentrations of study drugs at time points specified in the PK Time and Events Schedule 1B and processed, handled and identified according to the laboratory manual. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of niraparib and abiraterone using a validated, specific and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method under the supervision of the sponsor's Department of Bioanalysis. If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

9.3.3. Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the sponsor in accordance with the current Clinical PK Guideline. Additional PK parameters and details of the PK analysis, including data handling rules and software used to perform PK analysis, will be provided in the Clinical Pharmacology Analysis Plan. Based on the individual plasma concentration-time data, using the actual sampling times, the following PK parameters will be derived for both niraparib and abiraterone:

C_{max}	maximum observed analyte concentration niraparib C_{max}
$[C_{max}/\ dose]_{niraparib}$	maximum observed analyte concentration niraparib C_{max} normalized by the $dose_{niraparib}$
t_{max}	the actual sampling time to reach the maximum observed analyte concentration
$AUC_{0\ 168h}$	area under the plasma concentration-time curve from time 0 to 168 hours post dosing
$[AUC_{0\ 168h}/dose]_{niraparib}$	area under the plasma concentration-time curve for niraparib from time 0 to 168 hours post dosing

9.4. Safety Evaluations

See Protocol Section 9.7, and specific instructions below for Combination 3.

Adverse Events

Adverse events must be reported according to the instructions in Protocol Section 12.

During the PK Assessment Phase, all AEs (serious and non-serious) must be reported. Beginning with the Extension Phase (Day 8, after the 168-hour PK sampling), only SAEs must be reported.

Clinical Safety Laboratory Tests

Screening clinical laboratory tests should be performed centrally as outlined in Table 2. During the Extension Phase, clinical safety laboratory assessments (see Table 3) must be performed every 1-2 weeks for the first 3 cycles according to the timepoints in Time and Events Schedule 1A. From Cycle 4 onward, safety laboratory assessments will be at the discretion of the investigator according to routine practice. The safety laboratory tests may be performed centrally or locally.

The investigator must review laboratory results, document this review, and record any clinically relevant changes occurring during the study (all AEs during the PK Assessment Phase and SAEs only during the Extension Phase) 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.

Table 2: Screening Laboratory Tests (Central Laboratory)

Hematology Panel
-CBC (hemoglobin, white blood cell count, platelets, absolute lymphocyte count, and ANC)
Serum Chemistry Panel
-creatinine -glucose[a] -potassium
Liver Function Tests
-ALT -AST -alkaline phosphatase -serum total bilirubin (if abnormal, measure direct bilirubin)
Other Laboratory Tests
-serum albumin -serology (HIV and CD4 count if indicated[b], HBsAg, HepB core antibody, HCV antibody)
ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CBC=complete blood cell count; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HgbA1c=hemoglobin A1c; HIV=human immunodeficiency virus [a] Fasting glucose. [b]HIV and CD4 count should be only performed if indicated by prior medical history.

Table 3: Clinical Safety Laboratory Tests (Local or Central Laboratory)

Hematology Panel
-CBC (hemoglobin, white blood cell count, platelets, absolute lymphocyte count, and ANC)[a]
Serum Chemistry Panel
-creatinine -glucose -potassium
Liver Function Tests[b]
-ALT -AST -alkaline phosphatase -serum total bilirubin (if abnormal, measure direct bilirubin)

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CBC=complete blood count cell count

[a] CBC should be performed according to local label for niraparib: weekly during Cycle 1, monthly during Cycles 2-12, and then periodically after this time.

[b] Liver function tests should be performed according to local label for abiraterone acetate every 2 weeks (eg, on Day 1 and 15) during Cycles 1-3, and then monthly thereafter.

For suspected MDS/AML while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes) at screening. If needed, cytogenetic analysis will be done centrally for standardized evaluation. Testing completed as part of standard-of-care is sufficient if 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 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.

Other Safety Evaluations

Other safety evaluations are ECG, vital sign, physical examination, and ECOG PS evaluations. See Protocol Section 9.7, for descriptions.

9.5. Sample Collection and Handling

See Protocol Section 9.8, for sample collection and handling instructions.

9.6 Biomarkers

In Cohort 3, HRR gene alteration status is not required to determine study eligibility; however, it can be used to guide treatment during the Extension Phase.

Subjects can have HRR gene alteration status (Table 12) assessed by the sponsor from tumor tissue (archival) unless subjects have had a previous result from the sponsor's assays or a local test performed in a CLIA-certified or equivalent laboratory. If the subject has had a previous result from the sponsor's required assays or a local result from a CLIA-certified or equivalent laboratory,

then after the subject grants a release, the data can be reviewed for biomarker status. Local tests may be performed using tumor tissue, plasma, saliva, or blood.

Subjects testing positive for HRR gene alterations will be advised to continue treatment with niraparib and AAP. Subjects testing negative for HRR gene alterations or for whom HRR gene alteration status is unknown will be allowed to continue treatment with niraparib and AAP or AAP alone at investigator's discretion.

Table 12: Biomarker Panel

Genes	Definition
CCI	[redacted]

Adjustments to the biomarker panel of specific HRR gene alterations may be made based on evidence from emerging data. Any biomarker-related changes will be communicated to investigators via letter.

Additional biomarker tests may be performed on remaining tumor tissue samples (where allowed by local regulations). These additional tests may be used to help develop a diagnostic test to identify patients suitable for treatment with therapeutic regimens that include niraparib. Data generated may be used to understand response or resistance to niraparib and AAP combination therapy and data may be combined in a meta-analysis with data from other similar studies.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/WITHDRAWAL FROM THE STUDY

10.1. Completion

The subject is considered to have completed the study after discontinuing treatment in the Extension Phase for any reason and having had a follow-up (End-of-treatment) safety assessment or the subject is lost to follow-up.

10.2. Discontinuation of Study Treatment

Subjects who discontinue the study drugs should complete the EoT visit within 30 days (±7 days) of the last dose of study drug or prior to administration of a new anti-prostate cancer therapy, whichever occurs first. The subject's study treatment will be discontinued if:

- The investigator or sponsor believes (eg, for safety or tolerability reasons such as an adverse event) that it is in the best interest of the subject to stop treatment (refer to Protocol Section 6.2)
- The investigator believes the subject is no longer receiving clinical benefit from continued treatment
- Withdrawal of consent for continued treatment (subject's decision to discontinue for any reason).
- The sponsor terminates the study

In the event of early study completion or study termination by the sponsor, (whether or not the study endpoints are met), the sponsor will continue to provide study treatments until unequivocal disease progression, unacceptable toxicity, or an alternate method is in place to avoid treatment interruption.

10.3. Subject Withdrawal From the Study

The subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Investigator's decision

10.4. Withdrawal from the Use of Research Samples

See Protocol Section 10.4.

11. STATISTICAL CONSIDERATIONS

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 PK for Combination 3 is outlined below. Specific details will be provided in the Clinical Pharmacokinetic Analysis Plan.

11.1. Sample Size Determination

The sample size calculation for Combination 3 is based on statistical estimation enabling the study to provide an estimate on the magnitude of the relative BA between the test formulations and reference formulation with a precision close to the equivalence limit of (80%, 125%).

Based on the study data under single dose condition (212082PCR1007/abiraterone and TESARO-GSK 3000-01-004 Tablet Pilot BA/Niraparib Assumption at Table 4), a sample size of 30 PK evaluable subjects (15 per arm) will provide the point estimates of the GMRs between test and reference with following precisions (see Table 4). All subjects who have at least 1 noncompartmental PK parameter estimated will be considered PK evaluable

In total, approximately 68 subjects will be enrolled into Combination 3. Approximately 34 subjects (17 subjects per treatment group) will be randomized into Cohort 1, and 17 subjects will be assigned to each of Cohorts 2 and 3 (non-randomized) to ensure that at least 15 PK evaluable subjects from each arm complete the study.

Table 4: Precisions of the point estimates for GMR

Compound	Primary PK Parameter	Assumption on Inter-subject CV	90% CI
Abiraterone	C_{max}	64%	(70%, 143%)
	AUC	57%	(73%, 137%)
Niraparib	C_{max}	49%	(76%, 132%)
	AUC	59%	(72%, 139%)

11.2. Pharmacokinetic Analysis

11.2.1. Descriptive Statistical Analysis of Pharmacokinetic Data

All concentration-time data from subjects who have sufficient and interpretable drug exposure data will be included for the calculation of the noncompartmental PK parameters.

Data will be listed for all subjects with available study drug plasma concentrations per treatment. All concentrations below LLOQ or missing data will be labeled as such in the concentration data listings. Concentrations below LLOQ will be treated as 0 in the summary statistics and for the calculation of PK parameters. All subjects and samples excluded from the analysis will be clearly documented in the CSR.

Factors that may influence the study drug plasma concentrations (eg, vomiting, concomitant medication, fever, high pre-dose concentration) will be checked. If an influencing factor is present, a decision will be made by the PK/PD leader, whether to include or exclude the specific sample(s) or subject.

Reasons for exclusion of a subject or a sample from the analysis include, but are not limited, to the following:

- Pre-dose plasma concentrations equal to or higher than 5% of C_{max}
- Vomiting occurred at or before 2 times median t_{max} after study drug administration
- Noncompliance with study procedures affecting PK (eg, concomitant medication)

For each treatment, descriptive statistics, including arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for the plasma concentrations at each sampling time and for all PK parameters.

Graphical representations of the results will include, but are not limited to, the following graphs:

- Log-linear and linear-linear plasma concentration-time profiles for each individual
- Log-linear and linear-linear plasma concentration-time profiles for the mean values per treatment

11.2.2. Statistical Analysis of Relative Bioavailability

The primary PK parameters for statistical analysis will be C_{max} and $AUC_{0\ 168h}$ of niraparib and AA. All PK evaluable subjects will be included in the statistical analysis. PK parameters data for both abiraterone and niraparib will be log-transformed prior to the analysis.

Cohort 1. An analysis of variance model (ANOVA) with treatment as fixed effect will be applied to the log-transformed PK parameters data. The differences in means between the test formulations and the reference as well as the associated 90% CIs for the differences will be constructed from the model. The results will be back-transformed to derive the GMRs and the 90% CIs of abiraterone and niraparib, respectively, for the following pair: FDC1 regular-strength (G010) vs regular-strength SA.

Cohort 2. The same statistical analysis procedure as mentioned above will be applied to derive the GMRs and associated 90% CIs of abiraterone and niraparib, respectively, for the pair: FDC2 regular-strength (G012) vs regular-strength SA (from Cohort 1).

Cohort 3. The primary PK parameters for statistical analysis will be dose normalized (to 200 mg) C_{max} and $AUC_{0\ 168h}$ for niraparib; C_{max} and $AUC_{0\ 168h}$ of AA. The same statistical model as mentioned above will be applied to derive the GMRs and the 90% CIs of Abiraterone and Niraparib respectively between treatment arm in Cohort 3 vs. reference arm in Cohort 1.

Upon completion of PK assessment phase (up to Study Day 8) for the first 8 subjects enrolled from each arm in Cohort 1, statistical analysis for C_{max}, $AUC_{0\ 168}$ for both niraparib and abiraterone will be performed on the 16 subjects in a similar way as described above. The interim PK data will be summarized for informational purpose and will not require a database lock.

Cohort 2 and 3 will be started after the interim PK results readout in Cohort 1.

An interim analysis at N 8 for Cohort 2 following the same procedure as above may be performed by comparing Treatment C (Cohort 2) vs. Treatment A (Cohort 1A).

12. ADVERSE EVENT REPORTING

Refer to Protocol Section 12, for adverse event reporting procedures

13. PRODUCT QUALITY COMPLAINT HANDLING

Refer to Protocol Section 13, Product Quality Complaint Handling for instructions.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

See Protocol Section 14.1.2, for physical descriptions of SA niraparib, AA, and prednisone.

14.1.1. Niraparib/Abiraterone Acetate Fixed-Dose Combination Tablet

The FDC drug product formulations will be manufactured as immediate-release film-coated 50 mg niraparib/500 mg AA (low strength) or 100 mg niraparib/500 mg AA (regular strength)

tablets for oral administration containing 79.70 mg or 159.40 mg of niraparib tosylate monohydrate drug substance, equivalent to 50 or 100 mg niraparib free base, and 500 mg of AA drug substance.

The drug product will be manufactured and provided under the responsibility of the sponsor.

FDC1 regular strength (formulation number CJNJ67652000-G010) and FDC1 low-strength (formulation number CJNJ67652000-G009) tablets include the following excipients: hypromellose, sodium lauryl sulphate, lactose monohydrate, crospovidone, silicified microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate and Opadry color coating

FDC2 regular strength (formulation number CJNJ67652000-G012) and FDC2 low-strength (formulation number CJNJ67652000-G014) tablets include the following excipients: microcrystalline cellulose, sodium lauryl sulphate, lactose monohydrate, crospovidone, silicified microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate and Opadry color coating

FDC1 regular-strength and FDC1 low-strength tablets are manufactured using fluid bed co-granulation of AA and niraparib tosylate monohydrate.

FDC2 regular-strength and FDC2 low-strength tablets are manufactured using dry granulation and roller compaction of AA and niraparib tosylate monohydrate.

14.2. Packaging

See Protocol Section 14.2.2, for packaging information for SA niraparib and AA.

The FDC tablet formulations 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

See Protocol Section 14.4.1, and 14.4.3, respectively, for preparation, handling, and storage information for SA niraparib and AA.

14.5. Drug Accountability

Refer to Protocol Section 14.5, for instructions on drug accountability.

15. STUDY-SPECIFIC MATERIALS

Refer to Protocol Section 15, Study-specific Materials.

16. ETHICAL ASPECTS

Refer to Protocol Section 16, Ethical Aspects.

17. ADMINISTRATIVE REQUIREMENTS

Refer to Protocol Section 17, Administrative Requirements

REFERENCES

One new reference, Given 2017,[15] was added for Combination 3. See Protocol Section References.

Attachment 7: Long-term Extension Phase

After the primary analysis, the sponsor's decision, and subsequent notification to limit further data collection for a given combination, the Long-term Extension Phase for that combination will begin. The sponsor will continue to provide study treatment~~s~~ until subjects meet criteria for discontinuation of treatment (see protocol Section 10.2) or until further notification by the sponsor on a different means for continued supply of study treatment, whichever occurs first. Study treatment is defined as niraparib or the Janssen compound(s) or both in the given combination.

The Long-term Extension Phase for a given combination will begin when both the Amendment 7 is approved at the site and the sponsor has notified the site of the start of the Long-term Extension for that combination:

- Subjects who are still receiving niraparib in the Treatment Phase will be offered the option to continue to receive niraparib, either alone or with the accompanying study drug(s) in the respective combination.
- Subjects who are still receiving the specific combination drug(s) without niraparib in the Treatment Phase will be offered the option to continue to receive the specific combination drug(s). If the combination-specific drug(s) are commercially available, subjects might be offered to change to the commercially available drug.
- Subjects who have ended treatment and who are in the Follow-up Phase will be discontinued from the study and all data collection will cease. These subjects will be considered to have completed the study.

Study Treatment Administration

ADT administration

Refer to Section 6.1, of the protocol.

Study treatment

A treatment cycle is defined as per the Time and Event schedule of each given combination. Specifics of study treatment are provided in Protocol Section 6, pertaining to the Dosage and Administration for each combination. Sufficient study drug for each treatment cycle will be distributed as specified in Table 13. Dose modifications for toxicity are provided in Section 6.2, of the protocol.

If a subject was on a lower dose of niraparib or of the combination-specific drug(s) in the Treatment Phase of the combination cohort of the study, the subject should continue on the lower dose(s) in the Long-term Extension Phase.

Prohibitions and Restrictions

Refer to protocol Sections 4.4, 8.1, and 8.2.

Study Procedures for the Long-term Extension

All subjects continuing in the Long-term Extension Phase will follow the schedule of procedures provided in Table 13.

Sites should follow the subjects for disease assessment according to local practice and consult the local product labels (product IB or current protocol in case a local label is not available) for recommended laboratory/clinical monitoring. No efficacy data will be collected. Only SAEs will be collected into the global safety database as specified in Table 13, for long-term evaluation of safety until the end of study. 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 10.2 of the protocol, study treatment must be discontinued, and all data collection for that subject will end.

Table 13: Time and Events Schedule (Long-term Extension Phase)

Procedures	Comments	Long-term Extension Phase through End of Treatment Visit or termination of the study)
Informed consent	All subjects must sign the ICF for the LTE Phase	X (before starting the LTE)
Study Drug Dispensing		
Oral: Niraparib	Subjects still on niraparib will receive open label drug	Continuous; sufficient study drug until next visit will be dispensed
Oral: Abiraterone Acetate + Prednisone	Subjects in Combinations 2 and 3 still on AA will receive open label drug	Continuous; sufficient study drug until next visit will be dispensed
IV: Cetrelimab	Subjects in Combination 1 only	IV every 4 weeks in the clinic
Study drug compliance		X (via IWRS)
Clinical Laboratory (Local Laboratory)		
Hematology and blood chemistry		Per local practice and consult the local labels (product IB or current protocol in case a local label is not available) for niraparib and /or abiraterone acetate or the USPI/ EU SmPC. For cetrelimab, follow local practice for monitoring of other checkpoint inhibitors and consult product IB or current protocol.
Safety		
SAEs		Collection of SAEs; see Section 12.3.2, of protocol

AA abiraterone acetate; EU European Union; ICF informed consent form; IV intravenous; IWRS interactive web response system; LTE long term extension; SAE serious adverse event; SmPC Summary of Product Characteristics; USPI United States Package Insert.

Attachment 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 6 (29 October 2020)

The overall reasons for the amendment:

1. To close enrollment into Combination 1 (Cohorts 1A and 1B). Based on the results of the pre-planned futility analysis of biomarker negative subjects (Cohort 1B), a response rate of 13% was not achieved. For Cohort 1A, the Data Review Committee (DRC) reviewed data on the first 18 subjects enrolled. The overall response rate was 22% (95% confidence interval: 8%, 44%). Based on the current response rate, the chance of obtaining a 50% response rate in Cohort 1A, as hypothesized in the protocol by completing the cohort (n=30), is <1%. Therefore, the DRC recommended closing enrollment of Cohort 1A based on the low probability of success.
2. To give investigators the option of prescribing either niraparib and abiraterone acetate plus prednisone (AAP) or AAP alone during the Extension Phase in Combination 3. This change in study design is based on the outcome of the per protocol futility analysis conducted in the ongoing Phase 3 MAGNITUDE study (64091742PCR3001) of niraparib and AAP versus AAP for the treatment of subjects with metastatic prostate cancer, which showed there was no additional benefit of adding niraparib to AAP for the treatment of subjects without homologous recombination repair (HRR) gene alterations. No unexpected or new safety signals were identified by the Independent Data Monitoring Committee. CCI [redacted] These data support the combined daily administration of niraparib and AAP in subjects with metastatic castration-resistant prostate cancer (mCRPC) as planned during the 8-day PK Assessment Phase of Combination 3. Therefore, the Sponsor believes completion of the PK portion of Combination 3, and consideration of HRR status during extended exposure to the niraparib/AAP combination, preserves the ability to complete the main objective of Combination 3 while ensuring subjects and investigators have the information required to make long-term treatment decisions.
3. To revise safety monitoring and guidance based on updates to the niraparib core safety information.

Applicable Section(s)	Description of Change(s)

Rationale: Review of early response data suggests the combination of niraparib and cetrelimab is not likely to show benefit in men with mCRPC.

Applicable Section(s)	Description of Change(s)
Synopsis, Overview of Study Design, Statistical Methods; Time and Events Schedule 1; Time and Events Schedule 2; 3.1.1. Combination 1: Niraparib and Cetrelimab; 9.3. Pharmacokinetics and Immunogenicity (Combination 1); 9.7. Safety Evaluations; 11.3.1. Combination 1; 11.10. Futility Analysis; Attachment 5: Modified Schedule of Events for Combinations Closed to Enrollment	Added text that under Amendment 6, Combination 1 (Cohorts 1A and 1B) is closed to enrollment. Added information in text and into Attachment 5 that indicates a modified schedule of assessments will be followed for subjects in Combination 1; Time and Events Schedules 1 and 2 no longer apply. Added text indicating that only exploratory statistical analyses will be performed on efficacy data collected from subjects in Combination 1. Added text describing the analyses that resulted in the decision to close Combination 1. Modified Attachment 5 to allow it to be used for any combination that is closed to enrollment.
Rationale: Futility analysis results from the MAGNITUDE Study (64091742PCR3001) did not show additional benefit of adding niraparib to AAP in subjects without HRR gene alterations.	
1.1.3. Combination 3: Niraparib/AA FDC; 1.4.3. Combination 3: Niraparib/AA FDC; 3.3.3. Combination 3: Niraparib/AA FDC; 9.1.2.3. Combination 3; 9.5. Biomarkers; 16.1.3. Combination 3; Attachment 6 (A6): (A6) Time and Events Schedule 1A, (A6) 3.1. Overview of Study Design, Table 1, (A6) 6.1.2. Extension Phase, (A6) 9.1.4. Extension Phase, (A6) 9.6 Biomarkers	Added a summary of the MAGNITUDE Study futility analysis CCI [redacted] supporting the combined administration of niraparib and AAP during the PK Assessment Phase. Added text indicating that during the Extension Phase, subjects will be allowed to continue niraparib and AAP or AAP alone at the investigator's discretion guided by biomarker status and tolerability of the treatment. Added text indicating that, if not already known, biomarker status assessment is recommended, and results can be used to guide further treatment decisions during the Extension Phase.
Rationale: Hypertension has been reported with both niraparib and abiraterone acetate and to align with niraparib and AA product information.	
9.7. Safety Evaluations; Attachment 6, (A6) Time and Events Schedule 1A	Added additional timepoints for vital signs assessments and laboratory safety evaluations.

Applicable Section(s)	Description of Change(s)
Rationale: To align with the definitions and methods of contraception described in the Clinical Trials Facilitation and Coordination Group guidelines.	
4.2. Inclusion Criteria; 4.4. Lifestyle Considerations;	Inclusion criterion #12: Amended text to indicate that study participants must agree to use an adequate contraceptive method for the period indicated per Combination, as deemed appropriate by the investigator and as specified under Section 4.4. Lifestyle Considerations.
Attachment 6, (A6) Sec 4.1. Inclusion Criteria, (A6) 4.3. Prohibitions and Restrictions	Inclusion criterion #9 (for Combination 3): Amended text to indicate that study participants must agree to use an adequate contraception method for the period indicated. Added additional details on what are considered highly effective contraception methods in Section 4.3.
Rationale: The lowest dose of niraparib is 100 mg; further dose reduction is not allowed per protocol.	
6.2.1.1.1. Non-hematological Toxicities	Added instruction that niraparib must be discontinued for non-hematologic treatment-related Grade ≥3 toxicities lasting more than 28 days while the subject is administered niraparib 100 mg once daily.
Rationale: To align with recent core labeling changes for niraparib.	
6.2.1.1.1. Non-hematological Toxicities; 6.6.1.1.2. Hematologic Toxicity; 10.2. Discontinuation of Study Treatment	Added instructions that participants experiencing hypertensive crisis or who are symptomatic for or diagnosed with posterior reversible encephalopathy syndrome (PRES) should discontinue treatment with niraparib. Added/clarified dosing modification instructions for participants who experience inadequate recovery of platelet counts, neutrophil counts, and/or hemoglobin levels, or who develop acute myeloid leukemia or myelodysplastic syndrome.
Rationale: To allow enrollment of subjects whose tumors have alterations in genes outside the DNA repair pathway (eg, cyclin-dependent kinase 12 gene).	
Throughout protocol	For Combination 3, replaced DRD with HRR (homologous recombination repair).
Attachment 6, 9.6. Biomarkers, Table 12	Added Table 12 Biomarker Panel. Added that additional biomarker tests may be performed on remaining tumor tissue.
Rationale: To align with product information.	
6.3. Treatment of Overdose	Added instructions for the treatment of subjects who experience an overdose of niraparib, AA, or prednisone.
Rationale: To align with Janssen protocol template and current study procedures.	

Applicable Section(s)	Description of Change(s)
9.3. Pharmacokinetics and Immunogenicity (Combination 1); 12. Adverse Event and Serious Adverse Event Reporting; 12.1.1. Adverse Event and Serious Adverse Event Definitions and Classifications; 12.2. Special Reporting Situations; 12.3.2. Serious Adverse Events; 12.3.3. Method of Detecting Adverse Events and Serious Adverse Events; 12.3.4. Follow-up of Adverse Events and Serious Adverse Events; 13. Product Quality Complaint Handling; 13.1. Procedures; 14.4. Preparation Handling, and Storage; 14.4.2. Cetrelimab; 17.3. Subject Identification, Enrollment, and Screening Logs; 17.8. Monitoring; 17.9.2. Study Termination	Modified text related to adverse event, serious adverse event, product quality complaint, and other safety handling, reporting and follow up. Added text to allow remote consenting and monitoring. Added text indicating genetic analyses will not be performed on blood samples collected for PK or immunogenicity assessments. New text added to describe methods of detecting adverse events. Added information regarding the preparation, handling, and storage of investigational product. Clarified that cetrelimab administration guidelines are in the pharmacy manual. Clarified that reports and communications related to the study will identify subjects by subject identification and age at initial informed consent. Added text clarifying that the sponsor reserves the right to close an individual cohort or combination, and that this will be communicated to sites through a letter to the investigator.
Rationale: To correct minor errors and inconsistencies.	
Throughout the protocol	Consistent notation has been applied when referring to abiraterone acetate (AA) plus prednisone (AAP). Updated abbreviations. Added reference to the new niraparib/AA FDC Investigator's Brochure and prednisone product information (RAYOS) and updated the reference for ZYTIGA product information.
10.1. Completion	Clarified the conditions under which subjects will be considered to have completed the Treatment Phase and study.
Attachment 6, Time and Events Schedule 1B, Sec 8.1. Prohibited Concomitant Therapies	PK sampling windows were added and clarifying footnotes added. Clarified restrictions regarding concomitant prednisone use.

COVID-19 Appendix (17 April 2020)

The overall reason for the appendix: to provide study-related guidance during the global coronavirus (SARS-CoV-2) pandemic.

Applicable Section(s)	Description of Change(s)
Rationale: For health and safety reasons during the SARS-CoV-2 pandemic, subjects may not be able to come to the study site for scheduled procedures. An Urgent Safety Measure, dated 31 March 2020, was applied to implement this COVID-19 Appendix.	
COVID-19 Appendix	The standalone Appendix provides guidance to investigators for managing study-related procedures during the SARS-CoV-2 pandemic.

Amendment 5 (04 March 2020)

The overall reason for the amendment: to add Combination 3, which will investigate the relative bioavailability and safety of niraparib plus abiraterone acetate administered in a fixed-dose combination tablet.

Applicable Section(s)	Description of Change(s)
Rationale: In parallel to Study 64091742PCR3001, the pivotal clinical study supporting registration of niraparib in combination with AA-P for the treatment of men with mCRPC (with and without DRD), the Sponsor is pursuing development of a fixed-dose combination (FDC) tablet formulation of niraparib and AA with the aim of simplifying the combination regimen by reducing the pill burden. Based on the recommended dose of AA and the recommended Phase 2 dose for niraparib under Study 64091742PCR1001, the combination of these 2 individual products would require patients to be treated with up to 6 pills per day with the further addition of 1 to 2 tablets of prednisone or prednisolone. The FDC tablet presentation would reduce the number of pills to 2 tablets per day instead of 6. Reducing the pill burden for patients on oral medications for cancer may improve compliance as cancer patients often take multiple oral medications for cancer and for other comorbid conditions. Due to the genotoxicity of niraparib, this relative BA of FDC will be evaluated in mCRPC patients, regardless of DRD status and prior line of therapy, but not in healthy volunteers. The objective is to evaluate the relative bioavailability (BA) of the FDC tablets (Combination 3) in comparison to the single agent combination after single-dose administration. The results will facilitate the decision for which formulation is selected for other clinical trials as appropriate.	
Synopsis; Throughout the protocol; References	Language referring to Combination 3 has been added in the appropriate sections of the protocol. Givens 2017 added to References
Attachment 6	Attachment 6 has been added, which outlines the rationale, design, and procedures associated with Combination 3
Rationale: Study design: A single dose of FDC will be given to subjects to generate PK parameters, ie, C_{max} and $AUC_{0\text{-}168h}$ over 7 days for the assessment of relative bioavailability compared to single agent combination. Subjects will then enter an extension phase of combined single-agent niraparib+abiraterone acetate tablets (plus prednisone/prednisolone) so they can continue to receive potential therapeutic benefit.	
Synopsis; Throughout the protocol	Language referring to Combination 3 has been added in the appropriate sections of the protocol.
Attachment 6	Attachment 6 has been added, which outlines the rationale, design, and procedures associated with Combination 3
Rationale: To allow positive DRD or CDK12 testing results from certified laboratories with sponsor review to confirm eligibility as acceptable for screening. This review of local results from certified laboratories will allow subjects with known DRD and CDK12 pathogenic alterations to begin screening procedures.	
4.1. Prescreening Eligibility Criteria; 4.2.1. Combination 1: Niraparib and Cetrelimab; 9.1.2. Prescreening Phase for Biomarker Evaluation 9.5. Biomarkers	Language has been added to indicate that DRD or CDK12 results from CLIA-certified or equivalent laboratories may be used to determine biomarker eligibility provided this is confirmed by sponsor's review.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that subjects with any CDK12 pathogenic alterations are eligible for Cohort 1. The sponsor's current blood and tissue assay is unable to distinguish between monoallelic and biallelic CDK12 alterations.	
Synopsis Hypotheses Part 2 and Overview of Study Design; Following Sections for Combination 1: Niraparib and Cetrelimab: 1.1.1., 2.2.1., 3.1., 3.1.1., 4.1., 4.2.1., 9.1.2.1., 9.5, Table 9, 9.5.3., 16.1.1.	Where CDK12 has been mentioned, it has been clarified that this refers to CDK12 pathogenic alterations.
4.1. Prescreening Eligibility Criteria; 9.5. Biomarkers;	Added that CDK12 status will be assessed by tissue assay until blood assay becomes available.
Rationale: For subject convenience and flexibility.	
Time and Events Schedule 1: Study Procedures and Assessments for Combination 1 (Niraparib and Cetrelimab); Table 11 Attachment 5- Modified Schedule of Events Under Amendment 4	Central or local laboratories may be used for safety laboratory assessments
Rationale: To continue to provide drug for study participants who are benefitting from treatment.	
3.1. Overview of Study Design; 10.2. Discontinuation of Study Treatment	Language has been added indicating the Sponsor will continue to provide study drug for subjects who are benefitting from treatment at the time of early study completion or study termination by the Sponsor.
Rationale: Standard Janssen language for exclusion criteria related to malignancy has changed.	
4.3. Exclusion Criteria	Exclusion criterion 3. has been updated with current protocol template language.

Amendment 4 (18 December 2019)

The overall reasons for the amendment: The overall reason for the amendment is to close enrollment in Combination 2 because the objective of evaluating the antitumor effect of the RP2D of niraparib and AA-P for the treatment of mCRPC (metastatic castration-resistant prostate cancer) has been achieved by the totality of internal and external data available. After an evaluation conducted by the Data Review Committee of the ongoing safety and efficacy from subjects enrolled to date, the safety profile for niraparib remains consistent with no new safety signals identified. Efficacy data from QUEST Combination 2, coupled with external data published on other PARP inhibitors, support that patients harboring BRCA1/2 alterations derive the most clinical benefit relative to other DRD genes evaluated. Evaluating BRCA and other DRD anti-tumor activity further in Combination 2 of the QUEST study is no longer warranted.

Combination 1 – The CDK12 gene was added to the accepted biomarker panel for eligibility to enroll into cohort 1A (BM+) of Combination 1 (niraparib + cetrelimab). The basis for this inclusion was data from the olaparib PROfound study. Metastatic castration-resistant prostate cancer patients who had CDK12 gene alterations treated with olaparib had a median rPFS of 5.09 months compared to an rPFS of 2.20 months on either abiraterone or enzalutamide, demonstrating that patients with CDK12 gene alterations achieved greater benefit from a PARP inhibitor compared to antiandrogen agents. Furthermore, Antonarakis et al. concluded that a proportion of these patients respond modestly to PD-1 inhibitors, potentially implicating CDK12 deficiency in immunotherapy responsiveness. Because CDK12 appears to define a distinctly immunogenic class of prostate cancer and also now that there is randomized clinical trial evidence that PARP inhibition confers an rPFS advantage versus standard of care hormonal therapy, the combination of these two independent mechanisms of action is expected to confer at least additive clinical benefit to the proposed eligible patient population.

Applicable Section(s)	Description of Change(s)
Rationale: All relevant sections of the protocol have been revised to indicate that Combination 2 is closed to further enrollment. This amendment will allow subjects already enrolled into Combination 2 to continue study medication while reducing study procedures and limiting data collection.	
Synopsis	A statement was added describing the closure of enrollment in Combination 2 under Amendment 4.
3.1.2. Combination 2: Niraparib and AA-P	The following statement was added: "**Study Continuation Under Amendment 4 for Combination 2. Under Amendment 4, Combination 2 has been closed to enrollment. Subjects already enrolled in Combination 2 can continue to receive study medication by following the procedures outlined in Attachment 5. The subject is considered to have completed the study after discontinuing treatment for any reason and having had a follow-up (End-of-treatment) safety assessment or the subject is lost to follow-up.**"
9.1.1. Overview; 12. Adverse Event Reporting	A statement was added to provide guidance for Combination 2 subjects continuing in the study under Amendment 4.
Rationale: To provide guidance for currently enrolled subjects in Combination 2 as to the updated Time and Events schedule.	
Synopsis	The following statement was added: "**Under Amendment 4, enrollment into Combination 2 is closed. Only subjects who have signed the informed consent form prior to the approval date of Amendment 4 will be allowed to complete screening and be enrolled if all prescreening inclusion/exclusion criteria for Combination 2 are met. Subjects already enrolled in Combination 2 can continue to receive study medication until documented disease progression or the subject discontinues the study treatment for any reason as described in Attachment 5. Under Attachment 5, study-related assessments will be per local practice, at the investigator's discretion, and limited data will be collected. Study procedures for Combination 2 subjects to be followed under Amendment 4 are outlined in Attachment 5. For all subjects in Combination 2, once Amendment 4 is approved, Attachment 5, which overrules the protocol body text, should be followed.**"

Time and Events Schedule 3	The following statement was added to the Time and Events Schedule 3: "**(To be replaced by the Modified Schedule of Events provided in Attachment 5 once Amendment 4 is approved**)".
Attachment 5	The Modified Schedule of Events in Attachment 5 was added and supersedes Time and Events Schedule 3 for subjects continuing the study in Combination 2.

Rationale: To amend the description of the statistical analysis for Combination 2 under Amendment 4.

Synopsis Statistical Methods	The following statement describing the statistical analysis for Combination 2 was added: "**With Combination 2 closed under Amendment 4 prior to reaching the originally proposed sample size, only exploratory statistical analyses will be performed on data collected from subjects enrolled in this combination. Details will be provided in the statistical analysis plan (SAP).**"
11.3.2. Combination 2: Niraparib and AA-P	The following statement describing the statistical analysis for Combination 2 was added: "**Exploratory analyses only will be performed on efficacy data collected from subjects enrolled in this combination, pending data availability. Details will be provided in the statistical analysis plan (SAP).**"

Rationale: Per ICH and GCP guidelines, the subject is to sign an updated informed consent form when trial procedures are modified.

Time and Event Schedule 1	The informed consent row was updated to include the Prescreening informed consent. Footnote "c" was modified to include the term Prescreening.
4.1. Prescreening Eligibility Criteria	Included a new requirement for subject to sign the prescreening informed consent indicating the subject understands the purpose of the study and procedures required to participate in the study.
9.1.2. Prescreening Phase for Biomarker Evaluation	Clarified the consent requirements for biomarker analysis.
16.2.3. Informed Consent	A statement was added to clarify the purpose of the prescreening informed consent and the screening informed consent. A statement was added regarding requirement for enrolled subjects to sign an updated informed consent form in order to continue in the study under Amendment 4.

Rationale: Solid organ transplant rejection and acute graft-versus-host disease have been reported in subjects treated with PD-1 inhibitors.

4.3.1. Combination 1: Niraparib and Cetrelimab	Criterion #9 was added to exclude subjects with a history of organ transplant, including allogeneic stem cell transplantation.

Rationale: Based on recent data that show patients with mCRPC and CDK12 gene alterations benefit from treatment with a PARP inhibitor and possibly with treatment with immunotherapy, patients will biallelic loss of CDK12 will now be permitted to be enrolled into cohort 1A (BM+) of combination 1 (niraparib + cetrelimab). This data strongly suggests that CDK12 appears to define a distinctly immunogenic class of prostate cancer and with the addition of the randomized clinical trial evidence that PARP inhibition confers an rPFS advantage versus standard of care hormonal therapy, the combination of these two independent mechanisms of action is expected to confer at least additive clinical benefit to the proposed eligible population.

Synopsis	Biomarker evaluations were updated to include CDK12.

	For Combination 1, the following statement was amended as follows: All subjects will be assigned to a cohort based on their biomarker status for DRD (ie, Cohort 1A=BM+ or Cohort 1B=BM-) **or BM+ for CDK12**, which will be determined during the prescreening phase using a blood or tissue assay.
Synopsis Hypothesis; 2.2.1. Combination 1: Niraparib and Cetrelimab	For Combination 1, the following statement was amended as follows: • "That **cetrelimab** ~~JNJ-63723283~~ inhibition of PD-1 complements the antitumor activity of the PARP inhibitor, niraparib, for effective and safe treatment of subjects with metastatic castration-resistant prostate cancer (mCRPC) and DNA-repair gene defects (DRD) **or CDK12 gene loss**. • The combination of niraparib and **cetrelimab** ~~JNJ-63723283~~ is safe and has antitumor activity in subjects with mCRPC who do not have DRD **or CDK12 gene loss**.
Synopsis Overview of Study Design; 1.1.1. Combination 1: Niraparib and Cetrelimab	Statement added to describe the rationale for including the CDK12 biomarker.
Time and Events Schedule 1	Footnote "a" was amended to include the CDK12 biomarker.
1.1.1. Combination 1: Niraparib and Cetrelimab	The following statement was amended: "The combination of the PARP inhibitor, niraparib, and the PD-1 inhibitor, cetrelimab, has the potential to benefit patients with mCRPC who may or may not have DRD **or CDK12 gene loss**." The following statement was deleted: "~~Taken together, these data suggest that the combination of a PARP inhibitor and a checkpoint inhibitor may be a potential treatment for patients with mCRPC, including those with DRD (ie BM+) to potentiate the response to the PARP inhibitor, as well as those without DRD (ie, BM-), by creating an environment that improves tumor responsiveness to treatment.~~"
3.1. Overview of Study Design	The following statement was amended: "This is a Phase 1b-2, multicenter, open-label study to select the RP2D of niraparib in combination with other anticancer agents, followed by dose expansion that will enroll adult subjects with mCRPC who are either BM+ or BM- for DRD **or BM+ for CDK12** (see Section 9.5, for description of biomarker-positivity criteria)."
3.1.1. Combination 1: Niraparib and Cetrelimab	The following statement was amended: "This combination study will enroll adult subjects with mCRPC who are either BM+ (Cohort 1A) or BM- (Cohort 1B) for DRD **or BM+ for CDK12** based on the sponsor's blood or tissue assay."
3.1.1. Combination 1: Niraparib and Cetrelimab; 3.3. Biomarker Rationale; 3.3.1. Combination 1: Niraparib and Cetrelimab; 16.1.1. Combination 1: Niraparib and Cetrelimab	Text updated with CDK12 biomarker were appropriate. DRD and CDK12 biomarker status will be evaluated at the prescreening visit. Eligible subjects are to be BM+ (Cohort 1A) or BM- (Cohort 1B) for DRD or BM+ for CDK12.
3.3. Biomarker Rationale	The following statement was amended: "Subjects who are BM+ or BM- for DRD **or BM+ for CDK12** may demonstrate different responses to treatment with niraparib combination therapy."
4.1. Prescreening Eligibility Criteria	Prescreening eligibility criterion #2 was modified to include the analysis of CDK12 for blood and tissue samples. The sponsor can review data to determine the CDK12 status procured from a subject's sample that was previously analyzed by the sponsor's assays.

4.2.1. Combination 1: Niraparib and Cetrelimab	Inclusion criterion #1 was modified as follows: "Must have determination of biomarker ~~status~~ **positive** for DRD or **CDK12 (biallelic)** ~~(either BM+ or BM -)~~ by the sponsor's blood or tissue assay. For Part 1 of the study, subjects can be dosed prior to assay results becoming available. Results are required prior to dosing for Part 2."
9.1.2.1. Combination 1: Niraparib and Cetrelimab	The following statement was amended as follows: "For Combination 1, subjects will be assigned to a cohort based on their biomarker status ~~(ie, BM+ or BM -)~~ **(DRD and CDK12 [biallelic])**. ~~Once approximately 30 subjects have been enrolled in a cohort, that cohort will close and no additional subjects will be added.~~
9.5. Biomarkers	Text has been updated to include the biomarker CDK12. A row has been added to the bottom of Table 8 to include CDK12 (Cyclin Dependent Kinase 12). The title of Table 9 has been amended to include CDK12. The content of Table 9 has been updated to show subjects who have other gene biallelic loss are eligible for Cohort 1A of Combination 1. Table 9 also shows subjects who have BRCA monoallelic pathogenic loss, other monoallelic pathogenic loss, or are negative for DRD are not eligible for Combination 1.
Rationale: To provide updated futility analysis results to investigators participating in this study.	
3.1.1. Combination 1: Niraparib and Cetrelimab; 11.2.1. Combination 1: Niraparib and Cetrelimab	Text amended to show futility analysis has been completed.
Synopsis; 11.10. Futility Analysis	The results of the futility analysis were added.
Rationale: To amend the guidance for the reporting of anticipated events.	
Attachment 3	Updated standard text for the reporting of anticipated events replaced the former instructions for the reporting of anticipated events.
Rationale: Minor changes, corrections, and errors were addressed throughout the protocol.	
All sections	JNJ-63723283 was changed to cetrelimab.
Title page	The study title was edited to include "**QUEST**".
Synopsis	The following statement amended: "The second combination **to be studied** ~~will be~~ **is** niraparib in combination with ZYTIGA® (abiraterone acetate) and prednisone (referred to as AA-P) (Combination 2)." The following statement was amended in 2 locations in the Synopsis: "Part 1 ~~will not~~ **was not** conducted for Combination 2, as the RP2D for niraparib plus AA-P was established in the sponsor study 64091742PCR1001." The following statement was amended in the Synopsis for consistency: "~~Part 1 will not be conducted for Combination 2, as the~~ **The** RP2D for niraparib plus AA-P was established in the **sponsor** Study 64091742PCR1001 **(see Section 1.3.2). Therefore, Part 1 (dose-finding)** ~~will not~~ **was not conducted in this study for Combination 2**."
Abbreviations	Abbreviations list updated to reflect updated content of the protocol.
3.1.2. Combination 2: Niraparib and AA-P	The following statement was amended in Section 3.1.2, for consistency: "The RP2D for niraparib plus AA-P was established in **the sponsor** Study 64091742PCR1001 (see Section 1.3.2). Therefore, Part 1 **was** not conducted in this study for Combination 2."

3.4. Safety Evaluation Criteria for Part 1; 3.5. Safety Evaluation Team (Combinations with Part 1)	"An" SET was replaced with "A" SET.
9.7. Safety Evaluations (Table 10 and Table 11)	Footnote "a" was amended to show that fasting glucose in Combination 2 is required at screening and during the treatment phase of the study.
References	Two new references were cited within the body of the protocol and added to the list of references (reference #3: Antonarakis E, Isaacsson-Velho P, Agarwal N, Et al and reference #8 deBono J, Fizazi K, Saad F, et al).

Amendment 3 (28 November 2018)

The overall reason for the amendment: The overall reason for the amendment is to investigate the use of a second niraparib combination therapy for the treatment of subjects with mCRPC and DNA-repair gene defects. The second combination therapy (Combination 2) consists of niraparib in combination with abiraterone acetate and prednisone (referred to as AA-P).

Applicable Section(s)	Description of Change(s)
Rationale: The protocol was modified in order to investigate the safe and effective use of Combination 2 (niraparib and AA-P) for the treatment of subjects with mCRPC and DNA-repair gene defects.	
Synopsis	Information on Combination 2 was added to the synopsis, including a summary of the endpoints, hypothesis, study design, and statistical methodology. Information specific for Combination 1 was identified.
Time and Events Table 1; Time and Events Table 3	Time and Events Table 3 outlining study procedures for Combination 2 was added. Clarified that Time and Events Table 1 is specific for Combination 1.
1. Introduction	Updated to include information on anticancer combination agent AA-P.
1.1. Background and Design Rationale	The recommended Phase 2 dose for Combination 2 was added.
1.1.2. Combination 2: Niraparib and AA-P	The rationale for combining niraparib and AA-P for the treatment of patients with metastatic prostate cancer was added in a new section.
1.3.2. Combination 2: Niraparib and AA-P	A summary of the available clinical information for AA-P was added in a new section.
1.4. Benefit/Risk Assessment; 1.4.1 Combination 1: Niraparib and JNJ-63723283; 1.4.2. Combination 2: Niraparib and AA-P	New section for benefit/risk assessment for both Combination 1 and Combination 2 was added. (Benefit/risk assessment for Combination 1 was previously in separate benefit/risk assessment document.)
2.1. Objectives and Endpoints; 11.3.2. Combination 2: Niraparib and AA-P	Endpoints for Combination 2 were added. Text was clarified to indicate information specific for Combination 1.
2.2.2. Combination 2: Niraparib and AA-P	Hypothesis for Combination 2 was added in a new section.
3.1. Overview of Study Design	Section edited to be applicable for both Combination 1 and Combination 2.

Applicable Section(s)	Description of Change(s)
3.1.2. Combination 2: Niraparib and AA-P; Figure 2	Overview of study design and schematic for Combination 2 was added in a new section.
3.2.2. Combination 2: Niraparib and AA-P	Dose selection rationale for Combination 2 was added in a new section.
3.3. Biomarker Rationale	Indicated that exploratory biomarkers collection will occur only for Combination 1. Added a cross reference to Section 9.5, to provide further information on cohort eligibility based on DRD status.
3.3.2 Combination 2: Niraparib and AA-P	Biomarker rationale for Combination 2 was added in a new section.
3.5. Safety Evaluation Team (Combinations with Part 1)	Clarified that the Safety Evaluation Team is only used for Part 1 of the study.
4.1. Prescreening Eligibility Criteria	Section edited so that criteria is applicable for both Combination 1 and Combination 2. As a result, Criterion 3 (specific for Combination 1) was relocated to Section 4.1.1.
4.1.1. Combination 1: Niraparib and JNJ-63723283	Inclusion criterion specific for Combination 1 was relocated from 4.1 to this new section.
4.1.2. Combination 2: Niraparib and AA-P	A prescreening criterion specific for Combination 2 was added in a new section.
4.2. Inclusion Criteria	Section edited so that criteria is applicable for both Combination 1 and Combination 2. As a result, criteria specific for Combination 1 (Criterion 4, 5, and 6) were relocated to Section 4.2.1.
4.2.1. Combination 1: Niraparib and JNJ-63723283	Inclusion criteria specific for Combination 1 were relocated from 4.2 to this new section.
4.2.2. Combination 2: Niraparib and AA-P	Inclusion criteria specific for Combination 2 were added in a new section.
4.3.2. Combination 2: Niraparib and AA-P	Exclusion criteria specific for Combination 2 were added in a new section.
6.1.2. Combination 2: Niraparib and AA-P	Instructions for the administration of AA-P were added were added in a new section.
6.2.1.1. Combination 1: Dose Modifications for Niraparib	Dose modification instructions applicable only to Combination 1 were identified.
6.2.2. Combination 2: Niraparib and AA-P	Dose modification instructions for AA-P were added in a new section, including information on management of non-hematologic toxicities, hepatic toxicities, and hypokalemia as well as information on treatment interruptions for procedures.
7.2. Combination 2: Niraparib and AA-P	Treatment compliance procedures for AA-P were added in a new section.
8. Prior and Concomitant Therapy; 9.5.5. Non-steroidal Anti-inflammatory Drugs and Antibiotics	Indicated that collection of NSAID and antibiotic use is for Combination 1 only. Also, the timing for the collection of this information was clarified.
8.1 Prohibited Concomitant Therapies; 8.1.1. Combination 1: Niraparib and JNJ-63723283; 8.1.2. Combination 2: Niraparib and AA-P	Section 8.1, was edited to include only medications prohibited for both Combination 1 and Combination 2. Live virus vaccine was relocated from 8.1.1 to 8.1 as it is prohibited in both combinations. Medications prohibited in Combination 2 were added in new Section 8.1.2.

Applicable Section(s)	Description of Change(s)
8.2.2. Combination 2: Niraparib and AA-P	Restricted concomitant medications specific for Combination 2 were added in a new section.
9.1.1. Overview; 9.3 Pharmacokinetics and Immunogenicity; 9.4. Pharmacokinetic /Pharmacodynamic Evaluations; 11.1 Analysis Populations; 11.4 Pharmacokinetic and Immunogenicity Analyses; 11.6 Pharmacokinetic /Pharmacodynamic Analyses	Indicated that pharmacokinetics and immunogenicity will be assessed for Combination 1 only.
9.1.2. Prescreening Phase for Biomarker Evaluation; 9.1.2.1: Combination 1: Niraparib and JNJ-63723283; 9.1.2.2. Combination 2: Niraparib and AA-P	Section 9.1.2. was edited to be applicable for both Combination 1 and Combination 2, and repetitive text was removed. Text specific for Combination 1 was relocated to new Section 9.1.2.1. Information for Combination 2 was added to new Section 9.1.2.2.
3.1. Overview of Study Design; 8. Prior and Concomitant Therapy; 9.1.5. End-of-Treatment Visit; 11.8. Safety Analyses; 12.3.1. All Adverse Events; 12.3.2 Serious Adverse Events; 12.3.4. Disease Progression and Death	Text was edited to indicate that AEs, SAEs, and concomitant medications should be collected until 30 days after the last dose of study drugs, unless the subject received subsequent therapy for Combination 2. Indicated that this information is collected for 100 days for Combination 1.
9.2.1. Evaluations	Indicated that evaluation of treatment response will be assessed by immune-related RECIST criteria for Combination 1 only.
9.5. Biomarkers; 9.5.1 Tumor Samples	Text was edited to be applicable for both Combination 1 and Combination 2. Also, indicated text only applicable to each combination.
9.5.3. Circulating Tumor DNA	Indicated that section is only applicable for Combination 1.
9.7. Safety Evaluations	Text was edited to be applicable for both Combination 1 and Combination 2. For subsection Clinical Safety Laboratory Tests, the laboratory tests that are specific for each combination were identified.
11.2.2. Combination 2: Niraparib and AA-P	Sample size determination for Combination 2 was added in a new section.
11.3 Antitumor Activity Analyses; 11.3.1. Combination 1: Niraparib and JNJ-63723283; 11.3.2. Combination 2: Niraparib and AA-P	Moved information specific for Combination 1 to new section 11.3.1. Added information for Combination 2 in new section 11.3.2.
11.10. Futility Analysis	Indicated that futility analysis will be performed only for Combination 1 only.
14.1.2. Combination 2: Niraparib and AA-P	Physical description of AA tablets and prednisone tablets was added in a new section.
14.2.2. Combination 2: Niraparib and AA-P	Description of packaging for AA tablets and prednisone tablets was added in a new section.
14.4. Preparation, Handling, and Storage; 14.4.1. Niraparib, 14.4.2. JNJ-63723283, and 14.4.3. AA	Section reorganized to include 3 subsections, one for each medication (Niraparib, JNJ-63723283, and Abiraterone Acetate). Information for AA was added to new section 14.4.3, including information on drug exposure in women who are pregnant or may potentially be pregnant.

Applicable Section(s)	Description of Change(s)
16.1.2. Combination 2: Niraparib and AA-P	Study specific design considerations for Combination 2 were added in a new section.
17.9.1. Study Completion/End of Study	A cross references to Section 3.1, was added to provide further information on the data reporting for each individual combination.
Attachment 4: Additional Information on CYP450 Drug Interactions	Websites with information on CYP450 drug metabolism were added to provide information on medications with the potential for drug-drug interactions with Combination 2.
Rationale: For Combination 1, information on entry criteria and study procedures was reworded for clarity, edited to align with current practices, or updated to add more flexibility.	
Time and Events Schedule 1	The header was edited and a footnote was added to indicate that subjects should enter the Screening Phase within 6 weeks of receiving a final DRD result. For the prescreening SAEs and deaths row, clarification was added that this information should only be collected if related to study procedures. For the inclusion/exclusion row, an 'X' was added in the Prescreening row which was inadvertently omitted in previous versions. The physical exam on Day 15 of Cycle 1 and Cycle 2 and vital signs on Day 15 of Cycle 1 have been removed as these assessments are no longer required after additional experience with the study drugs. For the clinical safety laboratory tests row, testing by central laboratory was added as an option for these tests. For the survival status row, the text describing the collection period was edited for clarity. For the AE/SAEs and concomitant medications row, a cross reference was added to the protocol section with complete information on this topic.
Time and Events Schedule 1; 9.5.1. Tumor Samples	Updated to allow collecting of archival tumor sample during Cycle 1, if not collected at screening.
Time and Events Schedule 1; 9.1.5. End-of-Treatment Visit; Section 11.8. Safety Analyses	The term 'anti-prostate cancer therapy' was replaced with 'subsequent therapy'.
Time and Events Schedule 2	PK and immunogenicity assessments should be taken at the designated timepoints on Day 1 of Cycle 3 to 4. 'Day 1' was added to the table, as this information was inadvertently not included in the previous versions.
2.1. Objective and Endpoints	The definition of CTC response was updated to align with the definition used in Combination 2.
4.1 Prescreening Eligibility Criteria	Criterion 4 was deleted, and this information was moved to Section 9.1.2.
4.1.1. Combination 1: Niraparib and JNJ-63723283	For Criterion 1, reworded text (changed eg to ie) to exclude prior treatment with experimental novel AR-targeted therapies that may not have a proven benefit for the treatment of mCRPC.
4.2. Inclusion Criteria	For Criterion 11, the 4-week wash-out requirement for AA-P was removed; however, the wash-out is still needed for other anti-androgens.
4.2.1. Combination 1: Niraparib and JNJ-63723283	For Criterion 4, reworded text (changed eg to ie) to exclude prior treatment with experimental novel AR-targeted therapies that may not have a proven benefit for the treatment of mCRPC.
4.3. Exclusion Criteria	A definition for uncontrolled hypertension was added to Criterion 12.
6.1.1. Combination 1: Niraparib and JNJ-63723283	The infusion instructions for JNJ-63723283 were updated to align with the latest version of the investigational product preparation instructions.

Applicable Section(s)	Description of Change(s)
6.2. Dose Modification and Management of Toxicity	Instruction that cycle days are fixed based upon Cycle 1 Day 1 regardless of dose interruptions or delays was added.
6.2.1.1.1. Non-hematological Toxicities; 6.2.1.1.2. Hematologic Toxicity	Section 6.2.1.1.1, was reworded for readability and also to clarify that niraparib is only available in 100 mg capsules, so only one dose reduction is possible. This information was also clarified in Table 4 in Section 6.2.1.1.2.
9.1.3. Screening Phase	Text was updated to allow the screening physical exam and screening PSA laboratory evaluation to be used for the Cycle 1 Day 1 assessments, if performed within 14 days of Cycle 1 Day 1.
9.5 Biomarkers	Table 8 was modified so that only the genes that qualify a subject as biomarker positive are displayed. The genes that do not result in the qualification of a subject as biomarker positive were deleted from this table. Added that HDAC2 is only detected by the blood-based assay.
9.5.1 Tumor Samples	Text was reorganized and edited to align with current study procedures.
9.5.2. Circulating Tumor Cells	Information on whole blood sample processing was removed as not applicable to this section.
9.7. Safety Evaluations	Clarified that HIV and CD4 count only need to be performed if indicated by a subject's prior medical history. As blasts are no longer clinically relevant, they were removed from the complete blood count differential.
10.2. Discontinuation of Study Treatment	Instruction was added that palliative radiation for bone pain may not be considered unequivocal clinical progression and requires medical monitor discussion. Clarification was added that data for survival and subsequent therapies needs to be collected after discontinuation of treatment.
11.3.1. Combination 1: Niraparib and JNJ-63723283	Clarified that the secondary endpoint is CTC response rate rather than CTC response.
11.8. Safety Analyses; 12.1.3. Severity Criteria; 15 Study Specific Materials	Text updated to reflect that toxicities can be graded by NCI-CTCAE version 4.03 or also by a later NCI-CTCAE version.
12.3.4. Disease Progression and Death	Instruction that disease progression, even if it results in death during the AE reporting period, should not be reported as an adverse event was expanded.
14.4.1. Niraparib	Added that niraparib capsules should be handled with gloves.
Rationale: A subject's biomarker status may be determined by a blood or tissue assay (when the tissue assay is available for study use) for both Combination 1 and Combination 2.	
Synopsis; 3.1.1. Combination 1: Niraparib and JNJ-63723283; 5. Treatment Allocation and Blinding; 4.2.1. Combination 1: Niraparib and JNJ-63723283; 9.1.2. Prescreening Phase for Biomarker Evaluation	Updated text to state that biomarker status for DRD can be also be determined by a tissue assay.
Time and Events Schedule 1	Updated the Biomarker panel for eligibility footnote to add a cross reference to Section 9.5, where more detail on biomarkers is provided. Updated archival tumor sample footnote to clarify that the archival tumor sample can be collected during Cycle 1 only if unable to collect during screening.

Applicable Section(s)	Description of Change(s)
4.1 Prescreening Eligibility Criteria	Criterion 2 was updated to reflect that biomarker status can be determined by a blood or tissue assay. A previous sample analyzed by a Sponsor assay can also be used to determine biomarker status.
4.2.1. Combination 1: Niraparib and JNJ-63723283	Criterion 1 was updated to reflect that biomarker status can be determined by a blood or tissue assay.
9.5. Biomarkers	Section updated to indicate that biomarker status can also be determined by tissue for Combination 1. Table 9 added to provide cohort eligibility in Combination 1 and Combination 2 based upon DRD status.
Rationale: The term DNA-repair anomalies has been updated to DNA-repair gene defects (DRD) to align with terminology currently used in the niraparib clinical development program.	
Throughout the document	The term DNA-repair anomalies was replaced with DRD.
Rationale: Minor changes, corrections, and errors were addressed throughout the protocol	
1. Introduction	Updated to include correct EMA approval date for niraparib.
1.1. Background and Design Rationale	Sentence on the strategy for the analyses and future study of potential combination therapies has been updated. Redundant sentence on the addition of future combinations was deleted. Doses administered in Phase 2 Study 64091742PCR2001 were corrected.
3.3.1. Combination 1: Niraparib and JNJ-63723283	New published data on mutational burden and anti-PD-L1 response of mCRPC tumors was added.
16.1.1. Combination 1: Niraparib and JNJ-63723283	Removed information already presented in Section 1.4.1, and provided a cross-link to this information instead.
References	Citations for new publications referenced in the protocol as a result of Amendment 3 were added.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (22 May 2018)

The overall reason for the amendment: The overall reason for the amendment is to identify that the JNJ-63723283 dose of 480 mg once every 4 weeks is the recommended Phase 2 dose (RP2D) and to remove the JNJ-63723283 240 mg once every 2 week dose regimen from Part 1 of the study. In addition, the amendment addresses feedback from investigators regarding inclusion and exclusion criteria that allows additional treatment options prior to study entry. No impact on subject safety is anticipated.

Applicable Section(s)	Description of Change(s)
Rationale: The JNJ-63723283 480 mg once every 4 weeks dose has been selected as a recommended Phase 2 dose for the single agent JNJ-63723283 study (Study 63723283LUC1001). Safety and pharmacokinetic (PK) equivalency between the 240 mg once every 2 weeks and 480 mg once every 4 weeks doses has been established. The extended dosing interval provides increased patient convenience with no anticipated effect on safety.	
Synopsis: Overview of study design; Time and Events Schedule 1; Time and Events Schedule 2; 3.1.1. Combination-1: Niraparib and JNJ-63723283; Figure 1: Schematic for Combination 1; 3.2.1. Combination-1: Niraparib and JNJ-63723283; 6.1.1. Combination-1: Niraparib and JNJ-63723283: Table 4 Study Treatments	Text related to observations, assessments, and administration of the JNJ-63723283 RP2D dose 240 mg once every 2 weeks removed throughout the protocol.
3.2.1. Combination-1: Niraparib and JNJ-63723283	Text clarified that the JNJ-63723283 480 mg once every 4 weeks dosing schedule was selected as it is an RP2D in the JNJ-63723283 single agent study (Study 63723283LUC1001) and is preferable to the 240 mg once every 2 weeks dosing for subject convenience.
Rationale: To address feedback from principal investigators and to allow additional standard-of-care options prior to study entry.	
4.3. Exclusion Criteria	Criterion 9 for prohibition against prior radium treatment or treatment with other therapeutic radiopharmaceutical for prostate cancer was removed.
4.3.1. Combination-1: Niraparib and JNJ-63723283	Criterion 1 for prohibition against prior treatment with sipuleucel-T was removed. Criterion 2 was updated to remove the prohibition against prior therapy with anti-CTLA4.
Rationale: To address the transition of subjects enrolled into the JNJ-63723283 240 mg every 2 week regimen to the JNJ-63723283 480mg every 4 weeks regimen.	
3.1.1. Combination-1: Niraparib and JNJ-63723283	Text added to indicate that subjects enrolled into the JNJ-63723283 240 mg every 2 week regimen under a prior version of the protocol should be transitioned to JNJ-63723283 480mg every 4 weeks once the protocol amendment and revised informed consent form are approved at the site, as required by local regulations.

Applicable Section(s)	Description of Change(s)
Rationale: To provide for subject convenience as biomarker status does not determine cohort in Part 1 of the study.	
4.2. Inclusion Criteria; 9.1.2. Prescreen Phase for Biomarker Evaluation	Criterion 4 and subsequent text revised to indicate that subjects can be dosed prior to biomarker assay results becoming available in Part 1. Results are required prior to dosing for Part 2.
5. Treatment Allocation and Blinding	Direction provided to medical monitor or designee to review biomarker results in Part 2 in assigning subjects to the appropriate cohort.
9.1.3. Screening Phase	Text specifying subject assignment to cohort based on biomarker status at screening removed.
Rationale: To clarify that blood should not be drawn if there are no circulating tumor cells (CTCs) at screening in order to prevent unnecessary blood draws for this exploratory outcome.	
Time and Events Schedule 1: Circulating Tumor Cells	Footnote "j" added to clarify that collection of subsequent CTC samples are required only if CTC ≥1 at screening.
Rationale: To provide flexibility for PK sample collection and for subject convenience.	
Time and Events Schedule 2	For Cycle 1 and Cycles 2-3, the time of sample collection was lengthened from 2.5 to 4 hours to 2.5 to 6 hours. For Cycle 1 Day 2, the time of sample collection was extended to all day on Day 2 (within 8 hours of the Day 1 end of infusion). For Cycle 1 Day 4 and Day 8, the time of sample collection was extended to ±1 day of the end of infusion on Day 1. PK sample collections removed at Cycle 5 Days 2, 4, and 8, Cycle 7 Days 1 and 15, and at Cycles 9-10 Days 1 and 15 and replaced by Day 15 collections (±2 days of the end of infusion on Day 1) at Cycles 1 and 2.
Rationale: To align with the other protocols in the niraparib program and ensure consistency of management of niraparib adverse events.	
6.2.1.2. Hematologic Toxicities	Dose interruption/modification criteria were modified to align with other niraparib protocols. Text regarding supportive care for multiple blood transfusions was revised. Text regarding weekly CBC counts in the event of an adverse event was removed. Text regarding instructions for diagnosis of myelodysplastic syndrome/acute myeloid leukemia was updated. Table 5 was revised to update the management of Grade 3 or second occurrence of Grade ≥3 toxicities.
Rationale: Development of JNJ-63723283 study drug in progress.	
14.1.1. Combination-1: Niraparib and JNJ-63723283	Text regarding development of lyophilized study drug added to allow for flexibility to move to another equivalent study drug formulation. New drug descriptions for JNJ-63723283 frozen liquid in vial and lyophilized product provided.
14.2.1. Combination-1: Niraparib and JNJ-63723283	New packaging descriptions for JNJ-63723283 vials provided.

Applicable Section(s)	Description of Change(s)
Rationale: Alignment of text with recent protocol template changes.	
Title page	Text updated that US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312)
Time and Event Schedule 1: Informed Consent	New footnote "b" clarified that the informed consent must be signed before first study-related activity.
9.7. Safety Evaluations	Replaced "clinically stable endpoint" with "clinically stable condition".
17.11. Use of Information and Publication	Added the text in bold: 'key assessment parameters of the study will be used to determine a coordinating investigator **for the study'**. Replaced "within 12 months of the availability of the final data.." with "within 18 months…" Revised the text beginning 'Authorship of publications...'
Rationale: Minor changes, corrections, and errors were addressed throughout the protocol.	
Time and Events Schedule 1: Biomarker panel for eligibility	New footnote "c" clarified that Part 1 subjects can be dosed prior to assay results but biomarker results are required prior to dosing in Part 2.
Time and Events Schedule 1: Fresh biopsy	Footnote "d" clarified that the screening visit biopsy can be performed up to 56 days before Cycle 1 Day 1 provided no active treatment was initiated during the time.
Time and Events Schedule 1: Treatment compliance	Treatment compliance will no longer be assessed on Day 15 of each cycle; therefore, the "X" on Day 15 (all cycles) has been removed.
Time and Events Schedule 1: Clinical safety laboratory tests	Per footnote" h" clinical safety laboratory tests are to be obtained on Cycle 1 and Cycle 2 Day 1 and Day 15 and on Day 1 for all subsequent cycles (or more frequently at investigator discretion). Day 15 assessments at Cycle 3, Cycles 4-12, and Cycles 13 and Beyond removed.
Time and Events Schedule 2	PK timepoint scheduled for preinfusion JNJ-63723283 (480 mg every 4 weeks) on Cycle 5 Day 15 removed.
Synopsis; 11.2.1. Combination-1: Niraparib and JNJ-63723283	Text revised to indicate at least 6 subjects to be initially enrolled in Part 1. Reference to cohorts and dose regimen 1 and 2 removed.
1. Introduction	Text updated to indicate European Commission approval of niraparib on 20 November 2017.
1.1.1. Combination-1: Niraparib and JNJ-63723283; 1.3.1. Combination-1: Niraparib and JNJ-63723283	Text revised to streamline history of Study 63723283LUC1001. Detailed text regarding the 240 mg once every 2 weeks and 480 mg once every 4 weeks removed.
2.1. Objectives and Endpoints: Table 2 Objectives and Endpoints for Part 2	"Baseline" changed to "screening" for consistency with assessment in Time and Events Schedule 1.
3.1.1. Combination-1: Niraparib and JNJ-63723283; 3.4. Safety Evaluation Criteria for Part 1	Text modified to clarify that a SET meeting will occur after at least 6 evaluable subjects have completed the safety assessment period.

Applicable Section(s)	Description of Change(s)
Synopsis: Overview of study design; 3.1.1. Combination-1: Niraparib and JNJ-63723283	Text corrected to read "The sponsor may choose to enroll subjects to additional dose regimens (ie, at least 6 additional evaluable subjects) with JNJ-63723283….".
4.2. Inclusion Criteria	Criterion 1 text clarified to 18 years of age or older. Criterion 13g modified to include aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x ULN. Text indicting "or" removed.
8.1.1. Combination-1: Niraparib and JNJ-63723283	Ipilimumab (CTLA-4) is considered an investigational agent and is covered in Section 8.1, (Prohibited Concomitant Therapies). Text regarding specific immunotherapy and ipilimumab in Section 8.1.1. removed.
9.2.2. Criteria	Bone disease progression criteria was updated to better align with PCWG3 criteria.
11.1. Analysis Population	Text clarified that the ITT and PK analysis populations included subjects who had received at least 1 dose of both study drugs.
11.9. Data Review Committees	Text added to specify that the Data Review Committee (DRC) charter will be provided to the members of the DRC.
14.2.1. Combination-1: Niraparib and JNJ-63723283	Text modified to indicate study drug to be packaged in kits with appropriate management throughout the supply chain process. Study drug will not be dispensed in child-resistant packaging.
Attachment 1	Title changed to "Guidelines for the management of Immune-related Adverse Events for JNJ-63723283" to highlight that management can evolve over time and that sites should also refer to institutional standard-of-care.
References	Investigator Brochure references streamlined. Subsequent references resequenced throughout document.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (07 December 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 FDA received 9 November 2017 and a comment from MHRA received 29 November 2017. Other minor changes were also made.

Applicable Section(s)	Description of Change(s)
Rationale: There are limited data regarding the potential for a PARP inhibitor and a checkpoint inhibitor to have clinical benefit in subjects who are biomarker-negative (BM-). Therefore, a futility analysis for the BM- cohort (Cohort 1B) in Part 2 was added to allow for the cohort to be stopped if less than 1 subject has a clinical response after approximately 10 subjects are enrolled.	
3.1.1. Combination 1: Niraparib and JNJ-63723283; 11.2.1. Combination 1: Niraparib and JNJ-63723283	Reference was added to a new section (Section 11.10) for the futility analysis for Cohort 1B
11.10. Futility Analysis	New section added to summarize the futility analysis to be performed for Cohort 1B (ie, BM- subjects).
Rationale: Weekly monitoring for complete blood counts (CBCs) was added to the first cycle of treatment to ensure the safety of subjects, given that niraparib has a known hematologic toxicity profile. In addition, subjects who are reported with Grade ≥3 hematologic toxicities will be required to have their CBCs monitored weekly until resolution.	
Time and Events Schedule 1; 9.7 Safety Evaluations	Updated to include weekly CBC testing for the first cycle of treatment.
6.2.1.2. Hematologic Toxicity	Weekly monitoring of CBCs was changed from “recommended” to “required and recommended for 28 days after restarting dose” for subjects reported with Grade ≥3 hematologic toxicities.
Rationale: The safety evaluation criteria for non-hematologic toxicities in Part 1 was amended to categorize all Grade ≥3 non-hematologic toxicities as dose-limiting, with a list of exceptions based on the known toxicities for the disease.	
3.4. Safety Evaluation Criteria for Part 1	The safety evaluation criterion for Grade ≥3 non-hematologic toxicities was amended to include all Grade ≥3 events as dose-limiting, except for the specified exceptions.
Rationale: The sponsor does not intend to explore doses of niraparib beyond 300 mg once daily, which is the maximum tolerated dose observed with single-agent treatment. Therefore, the sponsor has removed the statement that alternate doses and dose schedules may be explored.	
3.5. Safety Evaluation Team	The statement that the SET may consider exploration of alternate doses and dose schedules was removed at the request of MHRA.
Rationale: The retreatment criterion for JNJ-63723283 regarding platelet counts was amended to ensure subjects’ platelet counts returned to ≥50,000 cells/μL without receiving a platelet transfusion.	
6.2.2.1. Retreatment Criteria for JNJ-63723283	Table 6 was amended to clarify that platelet transfusions are not allowed to return subject’s platelet counts to ≥50,000 cells/μL.

Applicable Section(s)	Description of Change(s)
Rationale: The use of bone-strengthening agents is typical in this patient population (ie, mCRPC) and the sponsor does not prohibit their use. However, the protocol did not previously specify that bone-strengthening agents were permitted. The protocol has been updated to add language allowing for the use of bone-strengthening agents at the discretion of the investigator.	
8. Prior and Concomitant Therapy	A statement was added that bone-strengthening agents are permitted and the choice of agent is at the discretion of the investigator.
Rationale: Given that the sponsor's blood-based assay is developmental and still undergoing validation, the specific mutations that will be used to determine biomarker-positivity were removed.	
9.5. Biomarkers	Table 8 (and associated text) describing the criteria for biomarker-positivity was updated to include the genes of interest, but remove the specific mutations that may be used to assign a subject as biomarker positive.
Rationale: Minor error in Time and Events Schedule 2 was corrected.	
Time and Events Schedule 2	The table previously indicated that samples would be collected on Cycle 1 Day 15 for niraparib testing; however, this will not be done. The collections were removed from the table. Other minor amendments were made to the table.
Rationale: Minor errors were noted and corrected	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

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 intervention, 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 , MD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

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

Signature

User	Date	Reason
PPD	03-Aug-2021 19:44:01 (GMT)	Document Approval