Janssen Research & Development *

Clinical Protocol

A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Subjects with Metastatic Prostate Cancer

MAGNITUDE

Protocol 64091742PCR3001, Phase 3
Amendment 6

JNJ-64091742 (niraparib)

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

EudraCT NUMBER: 2017-003364-12

Status: Approved
Date: 30 September 2021
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-146329771, 7.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	22 October 2018
Amendment 1	10 April 2019
Amendment 2	30 September 2019
Amendment 3	12 February 2020
COVID-19 Appendix (v 1.0)	17 April 2020
COVID-19 Appendix (v 2.0)	11 June 2020
Amendment 4	03 July 2020
Amendment 5	29 January 2021
Amendment 6	30 September 2021

A summary of previous amendments is in Attachment 8.

Amendment 6 (30 September 2021)

Overall Rationale for the Amendment:

The overall rationale for this protocol amendment is to incorporate the changes made in the statistical analysis plan.

1. To provide an early assessment of treatment benefit on the secondary endpoints and to ensure that the integrity of the study with respect to longer term outcomes is not compromised, the analysis approach is updated to a group sequential method for testing secondary endpoints (OS, TCC and TSP) in Cohort 1 with 2 interim analyses and a final analysis.
2. To specify how CDK12 subjects from Cohort 2 will be analyzed.

Section Number and Name	Description of Change	Brief Rationale
Schema	Added a figure for the schematic overview of the study for Cohorts 1 and 2, and a figure for the schematic overview of the study for Cohort 3.	To align with current study procedures.
Synopsis	Updated the synopsis to align with the changes made to the body of the protocol.	Alignment with the body of the protocol.
2.2 Hypothesis	Updated to remove the hypothesis that Niraparib and AAP will demonstrate improved rPFS compared to placebo and AAP in subjects with L1 mCRPC with or without HRR gene alterations.	To align with the current statistical analysis plan.
9.7 Vital sign	Removed the requirement for a completely automated device for the measurement of blood pressure and pulse/heart rate.	To allow flexibility to use both automated and manual devices for the measurement of blood pressure and pulse/heart rate.
11 Statistical methods; 11.3 Efficacy Analyses	Updated to reflect the group sequential method for testing secondary endpoints (OS, TCC and TSP) in Cohort 1 with 2 interim analyses and a final analysis.	See above for the overall rationale for the amendment.
11 Statistical methods; 11.3 Efficacy Analyses; 11.10 Interim Analysis	Updated to clarify that 2 interim analyses and a final analysis are preplanned for the secondary endpoints with analysis timing based on the number of OS events observed.	See above for the overall rationale for the amendment.
11.1 Analysis Populations	Updated the definitions for the analyses sets.	To align with the current statistical analysis plan.
11.7 Patient-reported Outcomes Analyses	Updated the thresholds for definition of deterioration for Worst Pain (BPI Question #3), EQ5D HUI, EQ VAS.	

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor revisions are made for improved clarity. Other minor errors and inconsistencies are revised, and grammatical, formatting, or spelling changes were made. Abbreviations and references are updated as needed. Consistent notation has been applied when referring to the research objective for Cohort 3: to describe the clinical experience with the FDC tablets of niraparib and AA, plus prednisone in subjects with mCRPC and HRR gene alterations.	Minor changes, corrections, and errors are addressed throughout the protocol.

SYNOPSIS

A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Subjects with Metastatic 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. The objective of this study is to compare niraparib and abiraterone acetate (AA) plus prednisone (AAP) versus placebo and AAP for the treatment of subjects with various stages of metastatic prostate cancer. In addition, the clinical experience with the fixed-dose combination (FDC) tablet formulation of niraparib and AA will be evaluated. This protocol will describe the overall conduct of the study and is intended to act as a master protocol for the niraparib and AAP combination. The study will begin with niraparib in combination with AAP for subjects with first-line (L1) metastatic castration-resistant prostate cancer (mCRPC; defined as subjects who have not been treated with any therapy in the metastatic castrate-resistant setting, except for androgen deprivation therapy [ADT] and a limited exposure to AAP). The sponsor may amend this protocol in the future to investigate the niraparib and AAP combination in additional stages of metastatic prostate cancer. These additional populations would be included as separate cohorts and would be analyzed independently.

PRIMARY OBJECTIVE, ENDPOINT, AND HYPOTHESES

Primary Objective: To evaluate the effectiveness of niraparib and AAP compared to AAP and placebo, as determined by radiographic progression-free survival (rPFS).

Hypothesis

Niraparib and AAP will demonstrate improved rPFS compared to placebo and AAP in subjects with L1 mCRPC and homologous recombination repair (HRR) gene alterations or in subjects with a prespecified subset of HRR gene alterations.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of niraparib 200 mg once daily in combination with AA 1,000 mg once daily plus prednisone 10 mg, compared with AAP and placebo in subjects with metastatic prostate cancer. Subjects in each cohort will be randomized in a 1:1 ratio to receive either niraparib and AAP or placebo and AAP. In addition, there is a separate open-label cohort to obtain clinical experience data for the FDC tablet formulation of niraparib and AA.

The study will consist of 5 phases; a Prescreening Phase for biomarker evaluation only, a Screening Phase, a Treatment Phase, a Follow-up Phase, and an Extension Phase (either Open-label or Long-term, depending on Cohort assignment). Subjects will be assessed using the sponsor's required assays; however, subjects may also provide a previous result from the sponsor's required assays or local testing results from a Clinical Laboratory Improvement Amendments (CLIA)-certified (or equivalent) laboratory demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel. Subjects will be assigned to a cohort based on their biomarker status and stage of disease. A treatment cycle is defined as 28 days. Imaging will be performed at Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, and then every 12 weeks. All subjects will be monitored for safety during the Prescreening, Screening, and Treatment Phases, and for at least 30 days after the last dose of both study drugs. Treatment will be administered daily and is planned to be continuous until disease progression, unacceptable toxicity, death, or the sponsor terminates the study.

Cohort 1: Subjects with mCRPC and HRR gene alteration

Cohort 1 will evaluate the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AAP) and HRR gene alteration. The cohort will enroll approximately 400 subjects.

Cohort 2: Subjects with mCRPC and No HRR gene alteration

Cohort 2 will evaluate the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AAP) and who have no HRR gene alteration. The cohort may enroll approximately 600 subjects. A prespecified futility analysis was performed after approximately 200 subjects were enrolled and approximately 125 progression events had occurred in this cohort.

The prespecified futility analysis for Cohort 2 was performed and reviewed by the IDMC. The futility criteria were met, hence enrollment into Cohort 2 was closed and subjects (except for subjects with CDK-12 alteration) were unblinded.

Cohort 3: Subjects with mCRPC receiving the FDC of niraparib and abiraterone acetate

To evaluate the clinical experience with the FDC tablet formulation of niraparib and AA, a separate open-label cohort has been added to the study (Cohort 3). Up to approximately 100 subjects may be enrolled into Cohort 3 under the same inclusion/exclusion criteria and undergo the same study procedures as Cohort 1, except that subjects in Cohort 3 will receive open-label niraparib+AA as an FDC tablet formulation instead of as single agents.

Data from Cohort 3, which will not be part of the Intent-to-Treat (ITT) or Safety population of Cohorts 1 or 2, and will be described separately.

STUDY POPULATIONS

Randomized Analysis Set for Cohort 1: Randomized subjects in Cohort 1 will be used for efficacy analysis for Cohort 1.

Safety Analysis Set: The safety analysis set includes all randomized subjects who received at least 1 dose of study medication in Cohort 1 and Cohort 2. The safety analysis set will be used for evaluating safety and treatment compliance. Safety analysis will be performed separately by Cohort.

FDC Analysis Set: All subjects who were enrolled into Cohort 3 will be used for baseline and demographic data analysis, and their clinical experience will be described. All subjects who received at least 1 dose of study medication in Cohort 3 will be evaluated for safety

EVALUATIONS

- Efficacy evaluations include the following:

  Radiographic progression-free survival (rPFS; primary endpoint): evaluated by tumor measurements using CT or MRI scans and whole-body bone scans (^{99m}Tc). Scans will be collected and reviewed by a central vendor.

  Serum prostate-specific antigen (measurements at a central laboratory) evaluated by Prostate Cancer Working Group 3 (PCWG3) criteria.

  Survival status.

  Subsequent systemic therapy for prostate cancer.

Cancer-related radiation therapy or surgical procedures.

Symptomatic progression.

Patient-reported outcomes.

- PK evaluations. Blood samples to measure plasma levels of niraparib and its metabolite, M1 (if judged relevant), will be obtained on Day 1 of Cycles 2 through 7. Population PK parameters and derived exposure will also be determined for niraparib. Blood samples to measure plasma levels of abiraterone will be obtained pre-dose on Day 1 of Cycles 2 and 3.
- Biomarker evaluations: HRR gene alteration status will be evaluated from blood and tumor tissue (archival or recently collected) samples. Other exploratory biomarker analyses will also be performed where allowed by local regulations.
- Safety evaluations: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, clinical safety laboratory tests, Eastern Cooperative Oncology Group Performance Score, ECG, and other safety evaluations at specified timepoints described in Time and Events Schedule 1.

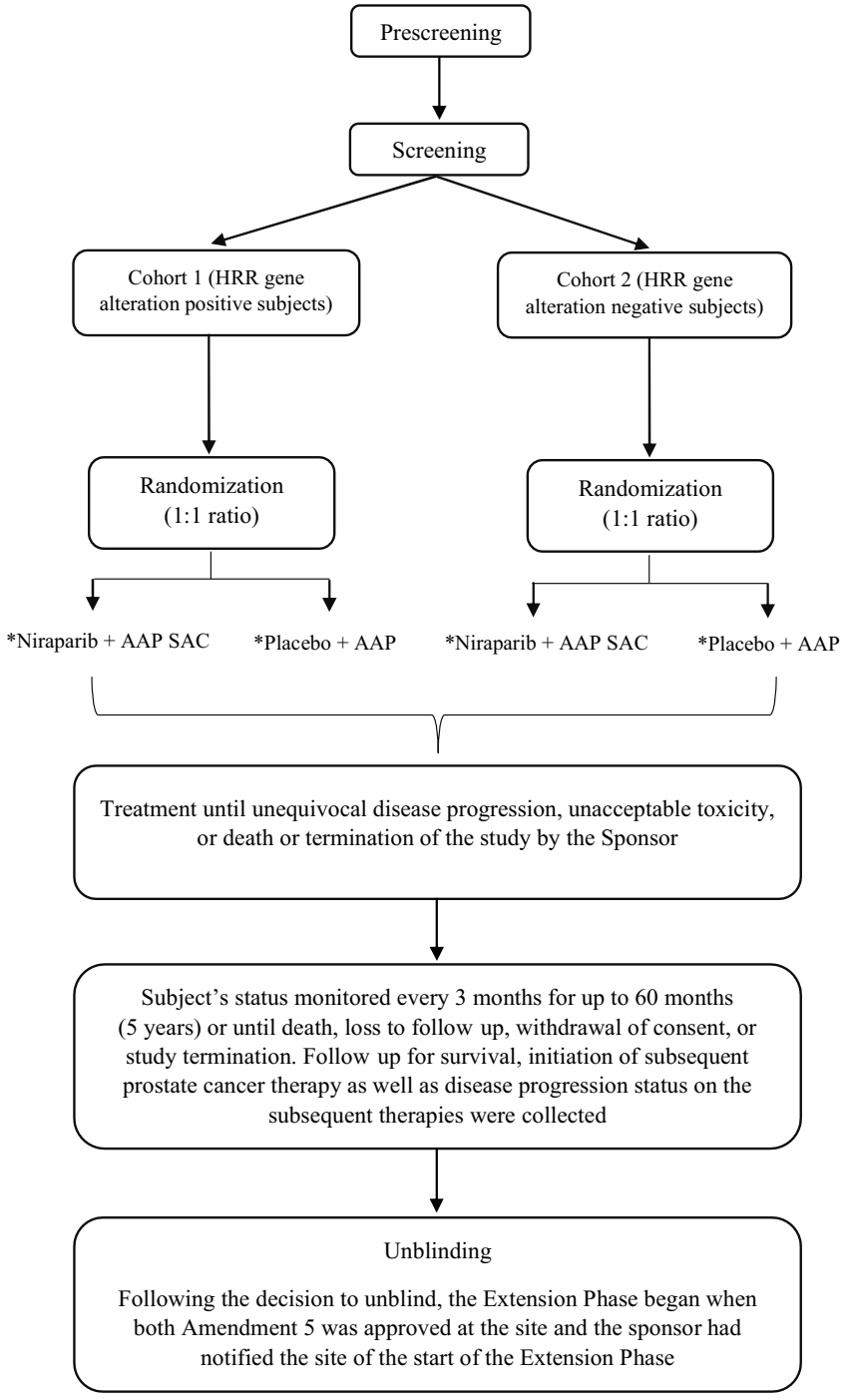
STATISTICAL METHODS

The planned sample size of approximately 400 subjects with HRR gene alterations (Cohort 1) will provide approximately 87% power to detect a HR of 0.65 for rPFS at a 2-tailed level of significance of 0.05. The sample size of the prespecified subset of subjects in Cohort 1 with BRCA 1 or 2 gene alterations (BRCA subgroup) is anticipated to be approximately 200 and will provide approximately 93% power to detect a HR of 0.5 for rPFS at a 2-tailed level of significance of 0.05. For the primary endpoint, the BRCA subgroup of Cohort 1 will be analyzed first. If statistical significance is reached in rPFS in the BRCA subgroup, then the entire population of subjects with HRR gene alterations (Cohort 1) will be tested.

The primary rPFS analysis will be performed when approximately 220 rPFS events have occurred in Cohort 1 and approximately 102 rPFS events for the BRCA subgroup.

SCHEMA

Figure 1: Schematic Overview of the Study Until the Start of the Extension Phase (Cohorts 1 and 2)



Prescreening
- Biomarker evaluation

Eligibility
- HRR gene alteration status
- CT/MRI documentation of disease metastasis
- Castrate level of testosterone GnRH level or surgical castration
- ECOG score 0 or 1
- Pain score ≤3 (BPI-SF Question #3)

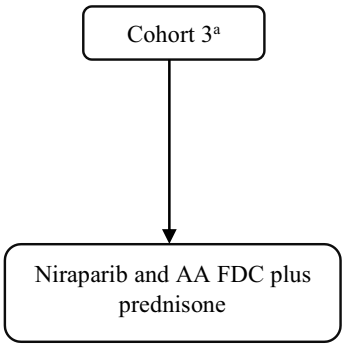
Randomization Strata
- Past taxane-based chemotherapy exposure
- Past AR-targeted therapy exposure
- Prior AAP use

Cohort 1 Strata
- Gene alteration (ie, BRCA1 or BRCA2 versus all other HRR gene alterations)

Treatment Cycle: 28-days

Key: AAP abiraterone acetate plus prednisone; AR androgen receptor; BPI-SF Brief Pain Inventory-Short Form; CT computed tomography; ECOG Eastern Cooperative Oncology Group; GnRH gonadotropin releasing hormone; HRR homologous recombination repair; LTE long-term extension; MRI magnetic resonance imaging; OLE open-label extension; SAC single-agent combination
*Niraparib 200 mg, abiraterone acetate 1,000 mg, prednisone 10 mg daily

Figure 2: Schematic Overview of the Study (Cohort 3)



Eligibility
Up to approximately 100 subjects with HRR gene alteration (approximately half with BRCA alterations)

[a] Began after enrollment into Cohort 1 (HRR gene alteration) and Cohort 2 (no HRR gene alteration) had completed and when the sponsor opened Cohort 3 for enrollment
Key: AA abiraterone acetate; FDC fixed dose combination; HRR homologous recombination repair
*Niraparib 200 mg, abiraterone acetate 1,000 mg, prednisone 10 mg daily

TIME AND EVENTS SCHEDULE 1: PROCEDURES AND ASSESSMENTS

See Attachment 5 and Attachment 6 for procedures to be followed during the Open-label and Long-term Extension Phases, respectively.

PHASE	Prescreening	Screening	Treatment Phase										Follow-up
CYCLE (treatment cycle is defined as 28 days)	Prior to the Screening Phase[a]	Up to 28 days prior to randomization unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycles 4 to 7	Cycles 8 to 12: Every cycle	Cycles 13 to 25: Every 2 Cycles; Beyond Cycle 25: Every 3 Cycles (eg, 28, 31, etc)	EoT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY			1[c]	15	1	15	1	15	1	1	1		
VISIT WINDOW				(±3 days)						(±3 days)		(+5 days)	(±4 weeks)
Informed consent	X												
Biomarker panel for eligibility (tissue and blood)	X												
Prescreening-related SAEs[d]	X												
Inclusion/exclusion criteria	X	X											
Demographics	X	X											
Medical history	X[e]	X											
Screening laboratory tests		X											
ECG, 12-lead		X											
Dispense study drugs			X		X		X		X	X	X		
Treatment compliance					X		X		X	X	X	X	
ECOG PS		X	X		X		X		X	X	X	X	
Physical examination		X	X	X	X		X		X	X	X	X	
Heart rate		X	X	X	X		X		X	X	X	X	
Blood pressure[f]		X	X (weekly)				X		X	X	X	X	
Clinical safety laboratory tests[g]		X	X (weekly)		X	X	X	X	X	X	X	X	
Serum PSA		X			X		X		X	X	X	X	
CT or MRI; Bone scan (^{99m}Tc)		X (within 6 wks of randomization)	*Imaging will be performed at Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, and then every 12 weeks[h].*									X	X[i]
Patient-reported Outcomes			See Time and Events Schedule 3 for details										
PK sampling			See Time and Events Schedule 2 for details										

PHASE	Prescreening	Screening	Treatment Phase										Follow-up
CYCLE (treatment cycle is defined as 28 days)	Prior to the Screening Phase[a]	Up to 28 days prior to randomization unless otherwise specified	Cycle 1		Cycle 2		Cycle 3		Cycles 4 to 7	Cycles 8 to 12: Every cycle	Cycles 13 to 25: Every 2 Cycles; Beyond Cycle 25: Every 3 Cycles (eg, 28, 31, etc)	EoT Visit (within 30 days of last dose)[b]	Every 3 months
CYCLE DAY			1[c]	15	1	15	1	15	1	1	1		
VISIT WINDOW				(±3 days)						(±3 days)		(+5 days)	(±4 weeks)
Circulating tumor cells		X[j]					X (if CTC ≥1 at baseline)[k]		X (if CTC ≥1 at baseline)[k]			X[k]	
Plasma for RNA			X[j]									X[m]	
Plasma for DNA			X[j,l]				X					X[m]	
Survival Status, Subsequent Therapy, and Disease Progression Status on the Subsequent Therapy[n]			*Collected continuously from randomization (including during the Follow up Phase)*										
Symptomatic Progression Events (see Section 11.3.1)[n]			*Collected continuously from randomization (including during the Follow up Phase)*										
AEs/SAEs and concomitant medications		*Collected continuously from screening until 30 days after last dose of both study drugs unless the subject received new anti prostate cancer treatment, has died, is lost to follow up, or withdraws consent*											
Related AEs/SAEs and associated concomitant medications		*Collected continuously from screening and followed until resolution*											
Medical Resource Utilization		*Collected continuously from screening up to and including the EoT Visit*											

AE=adverse event; CT=computed tomography; CTC=circulating tumor cells; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EoT=end of treatment; HRR=homologous recombination repair; ICF=informed consent form; MRI=magnetic resonance imaging; PK=pharmacokinetic; PSA=prostate specific antigen; RNA=ribonucleic acid; SAE=serious adverse event; ^{99m}Tc=technetium 99m; wks=weeks

a. **Prescreening Phase:** Subjects should enter the Screening Phase within 6 weeks of receiving a final HRR gene alteration 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. **Cycle 1 Day 1:** All subjects should commence treatment within 72 hours or 3 calendar days after randomization.

d. **Prescreening related SAEs:** During the prescreening phase, only SAEs related to the blood or tumor collection procedures should be reported from the time the ICF is signed until 30 days after the procedure occurs.

e. **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).
f. **Vital signs:** During cycles 1 and 2, blood pressure monitoring should occur weekly beginning on C1D1. Blood pressure monitoring can occur at a clinic visit or can be reported to the site by the subject, by home nurse, or by other method deemed reliable by the investigator.
g. **Clinical safety laboratory tests:** CBCs should be performed weekly for the first cycle of treatment. LFTs should be performed every 2 weeks for the first 3 cycles of treatment.
h. **CT or MRI; Bone scan:** CT/MRI should include imaging of the chest, abdomen, and pelvis. Subjects may have imaging performed within ±7 days of visits requiring images.
i. **CT or MRI; Bone scan:** Only for subjects who have not met radiographic progression and haven't initiated subsequent therapy (see Section 9.1.7).
j. **Exploratory Biomarker Analyses:** Collected and evaluated where feasible and allowed by local regulations.
k. **Circulating tumor cells:** Collected at Cycles 3, 5, 7, and EoT only if CTC is ≥1 at baseline.
l. **Plasma for DNA:** Cell pellet to be collected only at Cycle 1 Day 1.
m. **Plasma for RNA/DNA:** EOT samples should be collected when feasible
n. Survival Status, Subsequent Therapy, and Symptomatic Progression Events: May be obtained by telephone or chart review. May be obtained at a shorter interval than every 3 months during follow up if required for database lock.

TIME AND EVENTS SCHEDULE 2: PHARMACOKINETICS ASSESSMENTS

Phase	**Treatment Phase**							
Cycle	Cycle 2			Cycle 3		Cycles 4 to 7		
Cycle Day	1			1		1		
Visit Window	±3 Days							
Time	Predose	0	+1-3 h	Predose	0	Predose	0	≥3 h
Administration of study drugs		X			X		X	
PK blood samples for niraparib and its metabolite, M1	X		X	X		X	**or**	X
PK blood samples for abiraterone	X			X				

Notes:

- On Day 1 of Cycles 4 through 7, one PK sample is to be obtained either predose or at least 3 hours postdose. If the study visit is in the morning, subjects should refrain from taking the study drugs until after the PK sample is obtained at the investigative site. If the visit is in the afternoon, the subject should take their study drugs in the morning as usual and the PK sample will be collected during the study visit.
- The PK table applies both to subjects taking the separate study medications as well as the fixed-dose combination.
- The date and time of the PK samples and of the dose administered at the investigative site and prior dose taken at home should be recorded.
- For Cohort 3, the time of most recent predose meal should be collected on C2D1 and C3D1.

TIME AND EVENTS SCHEDULE 3: PATIENT-REPORTED OUTCOMES

Phase	Pre-screening	Screening	Treatment Phase														Follow-up	
Cycle	Prior to the Screening Phase	Up to 28 days prior to randomization unless otherwise specified	C1		C2	C3	C4	C5	C6	C7	Cycles 8 to 12		Cycles 13 24 Every 2 Cycles		Cycle 25 and after	EoT Visit (within 30 days of last dose)	Mos. 1 6	Every 3 Mos. up to 2 years after EOT
											Cycles 8, 10, 12	Cycles 9 & 11	Even No. Cycles (eg, 14, 16, 18, etc)	Odd No. Cycles (eg, 13, 15, 17, etc)	Every 3 cycles (eg, 25, 28, 31, etc)			
Cycle Day			1	15	1	1	1	1	1	1	1	1	1	1	1			
Visit Window				(±3 Days)												(±5 Days)	(±15 Days)	(±6 Weeks)
BPI SF #3[a]		X			X		X		X		X		X[b]		X[c] (every cycle)		X[a]	
BPI SF			X			X		X		X		X		X	X	X		X
FACT P			X		X	X	X	X	X	X		X		X	X	X		X
EQ 5D 5L			X		X	X	X	X	X	X	X			X	X	X		X
PRO CTCAE[d]			X		X	X	X	X	X	X		X		X	X	X		

BPI-SF=Brief Pain Inventory - Short Form; BPI-SF #3=BPI-SF Item 3; C=cycle; EoT=end-of-treatment; EQ-5D-5L=Euro-Quality-of-Life questionnaire; FACT-P=Functional Assessment of Cancer Therapy-Prostate questionnaire; PRO=patient-reported outcome; PRO-CTCAE=Patient-reported Outcomes Common Terminology Criteria for Adverse Events

Note: Details regarding PRO administration are provided in the PRO completion guide.

Note: Collection by phone can be done for any ePRO collection throughout the study, including during the follow-up phase.

[a] BPI-SF #3 is included in the full BPI-SF and; therefore, should only be completed at visits when the full BPI-SF is not collected.

[b] No on-site visits take place on even numbered cycles.

[c] BPI-SF#3 is to be collected remotely at every cycle when no on-site visit takes place (eg, Cycles 26, 27, 29, 30)

[d] PRO-CTCAE assessments will only be done in the United States, in English, and only during the Treatment Phase.

ABBREVIATIONS

^{99m}Tc=technetium-99m	^{99m}Tc=technetium-99m
AA	abiraterone acetate
AAP	abiraterone acetate plus prednisone
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated gene
BICR	blinded independent central review
BM	Biomarker
BP	blood pressure
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer gene
CLIA	Clinical Laboratory Improvement Amendments
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cells
ctDNA	circulating tumor deoxyribonucleic acid
DLT	dose-limiting toxicity
DRD	DNA-repair gene defects
DSB	double-strand breaks
EBRT	external beam radiation therapy
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
eDC	electronic data capture
EoT	end-of-treatment
EQ-5D-5L	Euro-QoL questionnaire
FACT-P	Functional Assessment of Cancer Therapy-Prostate questionnaire
FANCA	Fanconi anemia complementation group A gene
FDA	Food and Drug Administration
FDC	fixed-dose combination
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GnRHa	gonadotropin releasing hormone analog
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologous recombination repair
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	independent data monitoring committee
IEC	independent Ethics Committee
IRB	institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IWRS	interactive web response system
LTE	Long-term Extension
LFT	liver function test

MDS	myelodysplastic syndrome
MCID	minimum clinically important differences
mCRPC	metastatic castration-sensitive prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MRI	magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
OLE	Open-label Extension
OS	overall survival
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PCWG3	Prostate Cancer Working Group 3
PK	pharmacokinetic(s)
PQC	product Quality Complaint
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PRO-CTCAE	patient-reported outcome(s) Common Terminology Criteria for Adverse Events
PSA	prostate-specific antigen
SAP	statistical analysis plan
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TCC	time to initiation of cytotoxic chemotherapy
TEAE	treatment-emergent adverse event
TSP	time to symptomatic progression
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.[17] The sponsor licensed niraparib for the development of prostate cancer from TESARO, which is currently conducting clinical studies of patients with breast cancer, ovarian cancer, and non-small cell lung cancer. 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 (20 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).

ZYTIGA® (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.[25] The clinical benefits of AA in combination with prednisone or prednisolone (hereafter referred to as 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 (COU-AA-302), and patients with high-risk metastatic hormone-naïve (mHNPC) disease (LATITUDE).[9,13,27,29] 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).[23]

This is a study of niraparib in combination with AAP for the treatment of subjects with metastatic prostate cancer. This protocol will describe the overall conduct of the study and is intended to act as a master protocol for the niraparib and AAP combination. The study will begin with the evaluation of niraparib in combination with AAP for subjects with first-line (L1) metastatic castration-resistant prostate cancer (mCRPC; defined as subjects who have not been treated with any therapy in the metastatic castrate-resistant setting, except for androgen deprivation therapy [ADT] and a limited exposure to AAP as specified in Section 4). The sponsor may amend this protocol in the future to investigate the niraparib and AAP combination in additional stages of prostate cancer (eg, metastatic hormone-sensitive prostate cancer [mHSPC]). These additional populations would be included as separate cohorts and would be analyzed independently.

1.1. Background and Design Rationale

In patients with metastatic prostate cancer, DNA-repair anomalies are identified in approximately 15% to 20% of tumors.[7] At present, the role of DNA-repair anomalies as a prognostic biomarker is being investigated; however, patients with metastatic prostate cancer who have homologous recombination repair (HRR) gene alterations (eg, breast cancer genes [BRCA]1, BRCA2, ataxia telangiectasia mutated gene [ATM], Fanconi anemia complementation group A gene [FANCA], and others) may have a worse outcome.[4,7] In addition to having a prognostic role, the PARP

pathway has been identified as a potential drug target in prostate cancers that have HRR gene alterations.[1] In response to genotoxic insult, PARPs recruit proteins that promote DNA repair, which allows 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). Normally, DSBs are repaired through homologous recombination. If not repaired, DSBs result in cell death. When tumor cells with HRR gene alterations involving the homologous recombination pathway (eg, BRCA1, BRCA2) are treated with a PARP inhibitor, they are unable to efficiently and accurately repair DSBs, which creates a synthetic lethal condition.[3,11,33]

Clinical data from the TOPARP study, with the PARP inhibitor, olaparib (Lynparza®), have demonstrated potential efficacy in subjects with metastatic prostate cancer whose tumors have HRR gene alterations following treatment with chemotherapy and androgen receptor (AR)-targeted agents.[19] Initial data suggest improvement in both radiographic progression-free survival (rPFS) and overall survival (OS) in olaparib-treated subjects with either germline or somatic HRR gene alterations (ie, subjects with biomarker-positive [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, biomarker-negative [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, interpretation of this result is limited by 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.[19]

In addition to facilitating DNA-repair, dual roles for PARP in supporting AR activity have been observed in the preclinical setting. A study by Schiewer et al revealed that PARP-1 is a potent modulator of both AR function and response to DNA damage.[33] Primary human prostate tumor ex vivo cultures showed a significant antitumor response to PARP inhibition, which was correlated with diminished AR activity. 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 and 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.[8] The patients treated with a combination of olaparib and AAP had improved rPFS compared with those treated with AAP alone. This benefit was seen in both patients with and without HRR gene alterations. The sponsor has evaluated the single-agent combination of niraparib with AAP in the completed Phase 1b study

(Study 64091742PCR1001, BEDIVERE) and is currently investigating the relative bioavailability and safety of niraparib and AA as a fixed-dose combination (FDC) tablet in a Phase 2 study of subjects with mCRPC with DNA-repair gene defects (DRD) (Study 64091742PCR2002, QUEST, ongoing study). The sponsor is also conducting a Phase 1 bioavailability and bioequivalence study (Study 67652000PCR1001) to support development of the FDC tablet formulation.

Given the preclinical activity observed and clinical data available to date, the combination of the PARP inhibitor, niraparib, and the AR-targeted therapy, AA (in combination with prednisone, AAP) may have superior activity to AAP alone in patients with metastatic prostate cancer.

In this study, the sponsor will investigate niraparib in combination with AAP, compared to AAP alone (ie, placebo and AAP) for the treatment of subjects with metastatic prostate cancer in different disease settings. Initiating multiple separate clinical studies for different settings of metastatic prostate cancer would be time consuming and could delay promising therapies from reaching patients in need. The rapid implementation of new research findings within the protocol framework and study design is essential.[2] Protocols that allow multiple arms with different patient populations evaluating a similar combination are being utilized increasingly to evaluate therapies and have been shown to be substantially more efficient than traditional study designs.[35] Therefore, the sponsor will first investigate niraparib in combination with AAP in patients with L1 mCRPC (with and without pathogenic HRR gene alterations), although additional independent cohorts, which would utilize independent controls and statistical analyses, may be added in future to investigate other stages of prostate cancer (eg, mHSPC).

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.[16]

Niraparib as monotherapy has been approved in the US and EU for the treatment of ovarian cancer (see Section 1 for specific indications), regardless of mutation status.[37] In the TESARO Phase 3 registration NOVA study (NCT01847274) for subjects with ovarian cancer previously treated with platinum-based chemotherapy, the most common Grade 3/4 adverse events (AE) were thrombocytopenia (29%), anemia (25%), and neutropenia (20%),[37] which represent the identified important risk of hematological toxicity. The other identified risk is hypertension. Important potential risks include myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), second primary malignancy, embryo fetal toxicity, pneumonitis and thrombo-embolic events.

Niraparib is being evaluated as monotherapy in sponsor Study 64091742PCR2001 for the treatment of subjects with mCRPC and DNA-repair anomalies. Preliminary data from this study show that niraparib 300 mg as monotherapy for the treatment of subjects with mCRPC and DRD has a safety profile that is similar to the known safety profile of the drug for the treatment of platinum-sensitive ovarian cancer.[16] Hematologic toxicities are a known side effect of niraparib and were also observed in this study; however, the hematologic toxicities are manageable with standard outpatient care and dose interruption/reduction. Hypertension is also a known side effect

of niraparib; however, few cases (10.3%) have been observed up to the clinical cutoff of 06 February 2018 and no subject discontinued treatment due to hypertension. Efficacy was analyzed on the first 86 subjects enrolled up to the clinical cutoff of 06 February 2018 who had baseline and at least 1 post-baseline tumor measurements. Fifteen of these subjects (17.4%) had a response to treatment and approximately half (7 subjects, 12.1%) had measurable disease. A subgroup analysis was performed to evaluate subjects with biallelic loss of DRD. Thirteen subjects were included in the analysis and 7 subjects (53.9%) had a response to treatment.

Niraparib is also being explored in various company-sponsored combination studies, including Study 64091742PCR1001 (BEDIVERE) in combination with AAP (see Section 1.4 for preliminary safety data).

1.3. Summary of Available Nonclinical and Clinical Data for Abiraterone Acetate and Prednisone/Prednisolone

AAP is approved for the treatment of patients with metastatic prostate cancer.[38] 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.[15]

In clinical studies of subjects with metastatic prostate cancer, the most common AEs related to AA include peripheral edema, hypokalemia, urinary tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, dyspepsia, hematuria, hypertension, and fractures.[13,38] 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.

1.4. Summary of Available Clinical Data for Niraparib in Combination with Abiraterone Acetate and Prednisone/Prednisolone

The combination of niraparib and AAP administered as single agents was evaluated in a completed Phase 1b study of subjects with mCRPC (Study 64091742PCR1001, BEDIVERE). As of the clinical cutoff date of 06 February 2018, 16 subjects were included in the Safety Population; 12 subjects in the niraparib 200 mg and AAP cohort and 4 subjects in the niraparib 300 mg and AAP cohort.

No dose-limiting toxicities (DLTs) were reported in either dose cohort during Cycle 1 of the study (ie, the 28-day DLT evaluation period). In the niraparib 300 mg and AAP cohort, 2 subjects were reported with treatment-emergent AEs (TEAEs) of Grade 4 neutropenia on Day 1 of Cycle 2 and

these TEAEs were considered DLT-equivalent as they fell just outside of the DLT evaluation window. Both subjects with Grade 4 neutropenia recovered within 28 days of the event start date; however, upon review by the safety evaluation team (SET), the events were considered significant. In addition, 2 of the 3 evaluable subjects enrolled in the niraparib 300 mg and AAP cohort eventually required dose reduction to niraparib 200 mg for these toxicities.

Most subjects were reported with TEAEs; 83.3% in the niraparib 200 mg and AAP cohort versus 100% in the niraparib 300 mg and AAP cohort. The majority were Grade 1 or 2 in severity; however, slightly more Grade 3 or 4 events were observed in the niraparib 300 mg and AAP cohort (50% versus 75%, respectively). The most frequently reported TEAEs across both dose cohorts were nausea, fatigue, and back pain (37.5% each), constipation (31.3%), and vomiting (25%). The niraparib 300 mg and AAP cohort also had more SAEs (25%) and TEAEs leading to dose interruption/reduction (75%) than the niraparib 200 mg and AAP cohort (8.3% and 25%, respectively). AEs of special interest (AESIs) in this study are hematologic toxicities and hypertension and the niraparib 300 mg and AAP cohort were reported with slightly more of these events than the niraparib 200 mg and AAP cohort (50% versus 33.3%, respectively). No subject was reported with an TEAE with an outcome of death. A review of QTcF and QT intervals revealed no dose dependent effect or niraparib and AAP on electrocardiogram (ECG) parameters and no subject was reported with a TEAE of QT prolongation.

Preliminary PK data are available for 6 subjects from the niraparib 200 mg and AAP cohort. Exposures for both drugs were comparable with available data for both compounds administered as a single agent, suggesting the absence of a drug-drug interaction.

The preliminary data observed to date show that the combination of niraparib and AAP has a safety profile that is similar to the safety profile of each drug alone. Given that subjects in the niraparib 200 mg and 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.

1.5. Benefit/Risk Assessment

The combination of niraparib with AAP is hypothesized to have a positive benefit-risk profile when used for the treatment of patients with metastatic prostate cancer, as proposed for this study. This hypothesis 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). 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).
- The addition of niraparib to the AAP backbone regimen may improve initial disease control and long-term outcomes compared to AAP alone, as discussed in Section 1.1.
- While niraparib is an investigational agent in the metastatic prostate cancer population, it has been approved for the treatment of ovarian cancer. The safety profile of niraparib has been

characterized in clinical studies discussed in see Section 1.2. Preliminary data from sponsor studies suggest that the safety profile of niraparib in patients with metastatic prostate cancer is similar to that described in the Zejula® label.[37] Known toxicities for niraparib include gastrointestinal events, hematological events (ie, thrombocytopenia, neutropenia, anemia), and hypertension. These toxicities are managed by monitoring the appropriate laboratory values and making the appropriate medical interventions, such as dose interruptions. The protocol also includes a targeted monitoring plan and treatment guidelines to ensure appropriate management of toxicities.

- 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 1.4) show that niraparib and AAP may 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 when each drug is administered as a single agent.
- TEAEs and other safety data for the study will be monitored by the Independent Data Monitoring Committee (IDMC) and the sponsor's medical monitor during the conduct of the study, as described throughout this protocol.
- Established data with PARP inhibitors are fewer in patients with mCRPC without HRR gene alterations, as compared to those with HRR gene alterations (see Section 1.1). To ensure that subjects in Cohort 2 (ie, subjects with no HRR gene alterations) will not be exposed to the combination if there is no clear benefit, a futility analysis will be conducted when approximately 200 subjects have been enrolled and approximately 125 progression events have occurred in this cohort. (see Section 11.11).

Given that the anticipated toxicities of niraparib, AA, and prednisone 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 AA and prednisone for the treatment of patients with metastatic prostate cancer.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints/Assessments

The overall objectives and endpoints for the BRCA subgroup of Cohort 1 and the entire HRR altered population (Cohort 1) are provided in Table 1. In accordance with Protocol Amendment 5 and SAP Amendment 2, the preplanned futility analysis for Cohort 2 was performed and futility was met. Therefore, the combined Cohort 1 and 2 population is no longer applicable and will not be tested.

Table 1: Objectives and Endpoints/Assessments

Objectives	Endpoints/Assessments
Primary	
• To evaluate the effectiveness of niraparib and AAP compared to AAP and placebo	• Radiographic progression-free survival (rPFS)
Secondary	
• To assess the clinical benefit of niraparib and AAP compared to AAP and placebo	• OS • Time-to-symptomatic progression (TSP) • Time-to-initiation of cytotoxic chemotherapy (TCC)
• To characterize the pharmacokinetics (PK) of niraparib when given with AAP and abiraterone trough levels	• Observed plasma concentrations of niraparib and abiraterone and estimated population PK and exposure parameters for niraparib
• To characterize the safety profile of niraparib when given with AAP compared to AAP with placebo	• Incidence and severity of AEs • Clinical laboratory test results
Other	
• To evaluate other efficacy assessments and determine the clinical benefit of niraparib and AAP compared to AAP and placebo	• Time-to-PSA progression based on PCWG3 criteria[32] • PFS on first subsequent therapy (PFS2) • Time-to-pain progression
• To evaluate subject experience with disease-related symptoms • To evaluate overall health-related quality of life • To evaluate subject experience regarding treatment-related symptoms and tolerability	• Patient-reported outcomes (PROs) as assessed by the Brief Pain Inventory-Short Form (BPI-SF), the Functional Assessment of Cancer Therapy-Prostate (FACT-P), the EQ-5D-5L and PRO-CTCAE[a]
• To characterize the medical resource utilization profile of subjects treated with niraparib and AAP compared to AAP and placebo	• Medical resource utilization data associated with medical encounters
• To evaluate relationship between niraparib exposure, efficacy and safety measures, and exploratory response biomarkers	• Parameters describing exposure-response with efficacy (eg, rPFS), safety (eg, AEs), and response biomarker (eg, PSA) endpoints

AAP=abiraterone acetate plus prednisone; AE=adverse event; DNA=deoxyribonucleic acid; ECOG PS= Eastern Cooperative Oncology Group Performance Status; OS=overall survival; PK=pharmacokinetics; PCWG3=Prostate Cancer Working Group 3; PFS=progression-free survival; PRO=patient-reported outcomes; PRO-CTCAE=patient-reported outcome(s) Common Terminology Criteria for Adverse Events; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival

[a] PRO-CTCAE assessments will only be done in the United States and in English.

As Cohort 3 was added to provide descriptive data on the clinical experience with the FDC in subjects with mCRPC and HRR gene alterations, there is no hypothesis for Cohort 3.

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

2.2. Hypothesis

Niraparib and AAP will demonstrate improved rPFS compared to placebo and AAP in subjects with L1 mCRPC and HRR gene alterations or in subjects with a prespecified subset of HRR gene alterations.

There is no separate hypothesis for Cohort 3. The objectives for this cohort are described in Attachment 4.

3. STUDY DESIGN

3.1. Overview of Study Design

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

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of niraparib 200 mg once daily in combination with AA 1,000 mg once daily and prednisone 10 mg (2 x 5 mg), compared to AAP and placebo in subjects with metastatic prostate cancer. Subjects in each cohort will be randomized in a 1:1 ratio to receive either niraparib and AAP or placebo and AAP.

The study will consist of 5 phases; a Prescreening Phase for biomarker evaluation only, a Screening Phase, a Treatment Phase, a Follow-up Phase (see Section 9.1 for details), and an Extension Phase (either Open-label Extension [OLE] or Long-term Extension [LTE], see below and Attachment 5 and Attachment 6, respectively). Subjects will be assessed using the sponsor's required assays; however, subjects may also provide a previous result from the sponsor's required assays or local testing results from a Clinical Laboratory Improvement Amendments (CLIA)-certified (or equivalent) laboratory demonstrating a pathogenic germline or somatic HRR alteration in the gene panel listed in Table 4, Section 9.4. Subjects will be assigned to a cohort based on their biomarker status and stage of disease. Treatment will be administered daily and is planned to be continuous. For the purpose of scheduling visits, a treatment cycle is defined as 28 days. Imaging will be performed at Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, and then every 12 weeks. All subjects will be monitored for safety during the Prescreening, Screening, and Treatment Phases, and for up to 30 days after the last dose of both study drugs. Treatment will continue until discontinuation criteria are met (see Section 10.2).

In the event of study unblinding, early 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.

Following the decision to unblind, the Extension Phase will begin when both Amendment 5 is approved at the site and the sponsor has notified the site of the start of either the OLE or LTE. Details are provided in Attachment 5 and Attachment 6, respectively.

Under protocol amendment 4, after enrollment into Cohorts 1 and 2 is completed, an open-label cohort (Cohort 3) will be initiated to evaluate the clinical experience with the FDC tablet

formulation of niraparib and AA. Data from Cohort 3 will be described separately. Study procedures specific to Cohort 3 are described in detail in Attachment 4.

3.1.1. Cohort 1: Subjects with Metastatic Castration-resistant Prostate Cancer and HRR Gene Alteration

Cohort 1 will evaluate the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AAP as specified in Section 4) and HRR gene alteration. The cohort will enroll approximately 400 subjects with L1 mCRPC and HRR gene alteration (see Section 9.4 for description of biomarkers to be investigated and definition of biomarker-positivity).

3.1.2. Cohort 2: Subjects with Metastatic Castration-resistant Prostate Cancer and No HRR Gene Alteration

Cohort 2 will evaluate the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AAP as specified in Section 4) and who have no HRR gene alteration (see Section 9.4 for description of biomarkers to be investigated and definition of biomarker-negativity). The cohort may enroll approximately 600 subjects with L1 mCRPC without HRR gene alteration.

There is limited information on the efficacy of adding niraparib to AAP in subjects without HRR gene alterations (see Section 1.1). Hence, a futility analysis was performed after approximately 200 subjects were enrolled and approximately 125 progression events had occurred in Cohort 2. Futility was met for Cohort 2, therefore no additional subjects will be enrolled in this cohort. Further data collection for the subjects included in the futility analysis is described in Attachment 7. After final database lock and notification from the sponsor, subjects still receiving study treatment will move into the LTE (Attachment 6).

A study design scheme for Cohorts 1 and 2 is provided in Figure 1.

3.1.3. Cohort 3: Subjects With Metastatic Castration-resistant Prostate Cancer Receiving the Fixed-dose Combination of Niraparib and Abiraterone Acetate

To evaluate the clinical experience with the FDC tablet formulation of niraparib and AA, a separate open-label cohort has been added (Cohort 3).

Up to approximately 100 subjects with HRR gene alterations (approximately half of whom should have BRCA alterations) may be enrolled into Cohort 3.

Cohort 3 will be enrolled under the same inclusion/exclusion criteria and undergo the same study procedures as Cohorts 1 and 2, except that subjects in Cohort 3 will receive open-label niraparib+AA as an FDC tablet formulation instead of as single agents. Cohort 3 will not be part of the ITT or Safety Population but will be described separately. Information specific to Cohort 3 is described in Attachment 4. A study design scheme for Cohort 3 is provided in Figure 2

3.2. Study Design Rationale

AAP is approved for the treatment of patients with metastatic prostate cancer (ie, mCRPC in both the pre- and post-chemotherapy settings, as well as mHSPC).[23] Niraparib is approved for the treatment of ovarian cancer (see Section 1 for full indication), but is an investigational compound in the mCRPC setting. As described in Section 1.1, there is sound scientific rationale to investigate the combination of niraparib with AAP, based on evidence that PARP and the AR interact closely to modulate both AR function and response to DNA damage.[33]

The sponsor chose AAP as a background therapy for both treatment arms in each cohort for the following reasons:

- Reduce variability when assessing toxicities: AAP is an approved treatment for patients with metastatic prostate cancer and has a known safety profile. By ensuring that all subjects are on the same background therapy, the sponsor will be better able to assess the overall safety of the combination and the toxicities attributed to niraparib. If the sponsor allowed investigators to choose a preferred background therapy (ie, physician's choice), then the toxicities associated with the combination would be more difficult to interpret.
- Better evaluation of efficacy: by ensuring that all subjects receive the same background therapy, any additional benefit observed with the combination will be more easily assessed.
- Ensures that all subjects receive a current standard-of-care therapy for metastatic prostate cancer.

3.2.1. Selection of Dose

The dose of niraparib in this study is 200 mg once daily. This dose was selected based on data from the completed Phase 1b Study 64091742PCR1001 (BEDIVERE) that evaluated the RP2D for the combination of niraparib and AAP. At a dose of niraparib 200 mg, no DLTs were reported (see Section 1.4). Two out of 3 subjects in the niraparib 300 mg dose cohort were reported with DLT-equivalent toxicities of Grade 4 neutropenia early in the second cycle of treatment.

Supportive data from TESARO Study PN001 showed that antitumor activity was observed at various doses (from 80 mg to 400 mg once daily), as illustrated by the ≥50% inhibition of PARP activity in circulating peripheral blood mononuclear cells of subjects at steady state (ie, by Day 5 of Cycle 1).[30] The TESARO NOVA study evaluated a single-agent dose of niraparib 300 mg once daily as maintenance therapy in subjects with platinum-sensitive recurrent ovarian cancer.[22] However, dose reductions and interruptions have been common at that dose (65% and 27%, respectively), primarily related to hematologic and gastrointestinal toxicities.[16] Updated analyses from this study suggest that the 200 mg dose is associated with decreased incidence of treatment-related AEs, but does not compromise efficacy.[24] Based on the above information, a dose of niraparib 200 mg once daily has been selected for this combination study to maximize efficacy, while mitigating the potential for toxicity.

3.2.2. Blinding, Control, Study Phase/Periods, Treatment Groups

This is a randomized, double-blind, placebo-controlled study. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Randomization

procedures are discussed in Section 5.1. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur due to standard-of-care alone.

3.2.3. Biomarker Collection

In this study, biomarker samples (blood and tumor tissue [archival or recently collected]) will be collected and prospectively assessed during the Prescreening Phase to ensure that subjects enrolled into an HRR gene alteration cohort (eg, Cohort 1 and Cohort 3) are biomarker positive (as defined in Section 9.4). Subjects will be assessed using the sponsor's required assays. If the subject has had a sample previously analyzed by the sponsor's required assays or local result that shows a pathogenic germline or somatic HRR alteration for one of the selected genes (as listed in Table 4, Section 9.4, then the subject may enter Screening and be randomized (if eligible) after review of the results by the sponsor. Blood and tumor tissue should be collected and submitted for all subjects.

In addition to determining subject eligibility, exploratory biomarker assays may be performed (where allowed by local regulations) to better define changes in tumor status over time. Exploratory biomarker samples will be collected at the timepoints outlined in the Time and Events Schedule 1 to analyze the biological activity and resistance mechanisms of niraparib and AAP combination therapy before, during, and after treatment.

3.2.4. Medical Resource Utilization Data Collection

Treatment of subjects with metastatic prostate cancer with niraparib and AAP versus placebo and AAP may result in a higher number or duration of medical encounters; therefore, a comparison will be made across treatment groups.

4. SUBJECT POPULATION

Subjects over the age of 18 years (or the local legal age of consent) with metastatic prostate cancer are eligible for this study. Prescreening activities to determine biomarker status may occur any time prior to the Screening Phase; however, subjects should enter screening within 6 weeks of receiving their final biomarker status result from the sponsor.

The prescreening eligibility criteria, as well as the inclusion and exclusion criteria for enrolling subjects in this study are described in the following subsections. If there is a question about the criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not permitted.

4.1. Prescreening Eligibility Criteria

1. Signed informed consent form (ICF).
2. Criterion modified per Amendment 1

   2.1 ≥18 years of age (or the local legal age of consent)
3. Histologically confirmed prostate cancer.
4. Criterion modified per Amendment 4

   4.1 Can provide a blood sample for determination of HRR gene alterations.
5. Criterion modified per Amendment 4

   5.1 Willing to provide a tumor tissue sample (archival or recently collected) for determination of HRR gene alterations (see Table 4).
6. Metastatic prostate cancer in the setting of castrate levels of testosterone (ie, taking a gonadotropin releasing hormone analog [GnRHa], or history of bilateral orchiectomy at study entry).

4.2. Inclusion Criteria

1. Criterion modified per Amendment 3

   1.1 Criterion modified per Amendment 4

   1.2 Criterion modified per Amendment 5

   1.3 HRR gene alteration status (as identified by the sponsor's required assays or local testing for HRR gene alteration; see Section 9.4) as follows:

   a. Cohort 1: positive for HRR gene alteration
   b. Cohort 2: not positive for HRR gene alteration (ie, no HRR gene alteration)
   c. Cohort 3: positive for HRR gene alteration, see Attachment 4
2. Metastatic disease documented by positive bone scan or metastatic lesions on computed tomography (CT) or magnetic resonance imaging (MRI).
3. Criterion modified per Amendment 2

   3.1 Metastatic prostate cancer in the setting of castrate levels of testosterone ≤50 ng/dL on a GnRHa or bilateral orchiectomy as evidenced by prostate-specific antigen (PSA) progression or radiographic progression.
4. Able to continue GnRHa during the study if not surgically castrate.

5. Eastern Cooperative Oncology Group Performance Score (ECOG PS) Grade of 0 or 1 (see Attachment 1).

6. Score of ≤3 on the Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in last 24 hours).

7. Criterion modified per Amendment 2

   7.1 Clinical laboratory values at Screening:

   a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L.
   b. Hemoglobin ≥9.0 g/dL, independent of transfusions for at least 30 days.
   c. Platelet count ≥100 x 10^9/L.
   d. Serum albumin ≥3.0 g/dL.
   e. Creatinine clearance ≥30 mL/min either calculated or directly measured via 24-hour urine collection.
   f. Serum potassium ≥3.5 mmol/L.
   g. Serum total bilirubin ≤1.5 x upper limit of normal (ULN) or direct bilirubin ≤1 x ULN (Note: in subjects with Gilbert's syndrome, if 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).
   h. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x ULN.

8. Able to swallow the study drug tablets and capsules whole.

9. Criterion modified per Amendment 5

   9.1 While on study drug and for 3 months following the last dose of study drug, a male subject must agree to use an adequate contraception method as deemed appropriate by the investigator (specified in Section 4.4 Lifestyle Considerations) and agree not to donate sperm.

10. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.3. Exclusion Criteria

1. Prior treatment with a PARP inhibitor.

2. Criterion modified per Amendment 2

   2.1 Systemic therapy (ie, novel second-generation AR-targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy, or more than 4 months of AAP prior to randomization) in the mCRPC setting; or AAP outside of the mCRPC setting.

3. Criterion modified per Amendment 2

   3.1 For subjects who received 2 to 4 months of AAP prior to randomization for the treatment of mCRPC, evidence of progression by PSA (per PCWG3) during screening. These potential subjects are required to have 2 PSA values during the Prescreening and Screening Phases. The second PSA value should be within 2 weeks of randomization. If PSA rise is thought to be due to flare, the investigator should confirm that there is no radiographic progression. See Section 9.1.3 for full details.

4. Symptomatic brain metastases.

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

6. Other prior malignancy (exceptions: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤2 years prior to randomization, or malignancy that currently requires active systemic therapy.

7. 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.

8. Presence of uncontrolled hypertension (persistent systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of hypertension are allowed, if BP is controlled to within these limits by anti-hypertensive treatment.

9. 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.

10. Criterion modified per Amendment 5

    10.1 Active or symptomatic viral hepatitis or chronic liver disease (as evidenced by ascites, encephalopathy, or bleeding disorders secondary to hepatic dysfunction).

11. History of adrenal dysfunction

12. Known allergies, hypersensitivity, or intolerance to AA or niraparib or the corresponding excipients (refer to Investigator's Brochures).

13. Subjects who are receiving opioid analgesics at the time of screening.

14. Human immunodeficiency virus (HIV) positive subjects with 1 or more of the following:

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

15. Subjects who have had the following ≤28 days prior to randomization:

    a. A transfusion (platelets or red blood cells).
    b. Hematopoietic growth factors.
    c. An investigational agent for prostate cancer.
    d. Major surgery (sponsor should be consulted regarding what constitutes major surgery).
    e. Radiation therapy

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. Selected clinical information for each subject will also be reviewed by the sponsor prior to randomization to ensure that eligibility criteria have been met. 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 drugs are given such that he no longer meets all eligibility criteria, then the subject may be excluded from participation in the study. Sections 9.1.2 Prescreening Phase for Biomarker Evaluation and 9.1.3 Screening Phase, describe options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

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 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 after the last study medication administration.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Treatment Allocation

Subject information will be entered by the site into a central interactive web response system (IWRS) during the Prescreening Phase and each subject will be assigned a subject identification number. Blood and tumor tissue (archival or recently collected) samples will be collected and sent for testing for biomarker status using the sponsor's required assays.

If the subject has had samples previously analyzed by the sponsor's required assays, or other local test (CLIA certified or equivalent) that show a pathogenic germline or somatic HRR gene alteration (as listed in Table 4, Section 9.4), then after the subject grants a release, the data can be reviewed for biomarker status. The sponsor or designee will review the results of the biomarker testing and selected clinical information and will complete a pre-randomization eligibility review. Based on the biomarker testing results, subjects will be allocated to the appropriate cohort and will then move to the Screening Phase.

Subjects will be randomly assigned in a 1:1 ratio to receive either niraparib and AAP or placebo and AAP. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Randomization will be performed across all study sites using the IWRS. The IWRS will assign a unique subject identification number to each subject. The subject's identification number will be used on all study-related documents including electronic case report forms (eCRFs). A treatment number will also be assigned to each subject. This treatment number is the link between a subject's eCRF and blinded treatment group assignment. Subject identification numbers will not be reused. Subjects withdrawn from the study will not be replaced. All subjects should commence treatment within 72 hours or 3 calendar days after randomization.

For Cohorts 1 and 2, randomization will be balanced by using randomly permuted blocks and will be stratified by past taxane-based chemotherapy exposure (yes versus no), past AR-targeted therapy exposure (prior novel anti-androgen therapy, such as enzalutamide, apalutamide, darolutamide versus no prior novel anti-androgen therapy), and prior AAP use (yes versus no). For Cohort 1, stratification by gene alteration group (ie, BRCA1 or BRCA2 versus all other HRR gene alterations) will also be performed.

5.2. Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject in case of an emergency.

Under normal circumstances, the blind should not be broken until completion of the study or the IDMC recommendation for unblinding is accepted by the sponsor or the sponsor decides to unblind after the primary endpoint analysis is completed. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation before breaking the blind. A committee of investigators will be assembled to review requests for unblinding. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner. Subjects who have had their treatment assignment unblinded must discontinue study treatment, have an end-of-treatment (EoT) visit, and continue with follow-up evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, given that an interim analysis and a futility analysis are specified (see Section 11.10 and Section 11.11), the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those

authorized personnel and only for those subjects included in the interim and futility analyses as appropriate.

6. DOSAGE AND ADMINISTRATION

For the purpose of this study, 'study drugs' refers to niraparib, placebo, and AAP. All dosing information must be recorded in the eCRF. Supply of study drugs will be managed through the use of an IWRS. All study drugs, including AAP, will be provided directly by the sponsor.

6.1. Study Drug Administration

All subjects will receive AAP as standard-of-care therapy from a central supply while on the Treatment Phase of the study. Investigators should refer to the package insert/pharmacy manual for instructions regarding storage, handling, and administration of AAP.[38] 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 oral administration (total daily dose of 10 mg).

Subjects in each cohort will be randomized in a 1:1 ratio (see Section 5.1 for details) to receive either 200 mg niraparib or matching placebo.

Niraparib will be provided as 2 x 100 mg capsules for once daily oral administration. The placebo will be provided as capsules and will be matched in size, color, and shape to niraparib to maintain the study blind.

6.1.1. Dosing Instructions

Study drugs will be administered orally on an outpatient basis and a treatment cycle is defined as 28 days. Sufficient study drugs for each treatment cycle will be distributed on the first day of each cycle (see Time and Events Schedule 1). Subjects will begin taking study drugs on Day 1 of Cycle 1.

Subjects should take their daily dose of study drugs in the morning on an empty stomach. No food 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 or placebo alone, AAP alone, or both), then the missed dose(s) should only be replaced within the same day. For treatment modifications due to toxicities see Section 6.3.

Although not considered study medication, subjects who have not undergone surgical castration must continue to receive regularly prescribed GnRHa in order to maintain castrate levels of testosterone (≤50 ng/dL). The choice of GnRHa is at the discretion of the investigator and dosing should be consistent with the prescribing information. 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. Subjects are permitted to undergo a bilateral orchiectomy instead of ADT with a GnRHa during the study.

6.2. Special Dosing Instructions for Pharmacokinetics Visits

For PK sampling days on Cycle 2 Day 1 and Cycle 3 Day 1, study drugs should be taken at the site under the supervision of the investigator or designee and should not be taken at home on the morning of the visits. For PK sampling days on Cycles 3 to 7, study drugs should be taken at the site under the supervision of the investigator or designee if the visit is scheduled to occur in the morning or taken at home in the morning as usual if the visit is scheduled to occur in the afternoon. If a subject's study drug is interrupted (eg, for toxicity), the site should contact the sponsor for instructions regarding PK sample collection. Details of PK sampling days and times are provided in Time and Events Schedule 2. Additional details regarding PK sampling are provided in Section 9.2. Details of blood sample handling and storage procedures for PK are provided in the laboratory manual.

6.3. Dose Modification and Management of Toxicity

All dose interruptions and dose reductions (including missed doses) and the reason for the interruption/reduction are to be recorded in the eCRF. Note that cycle days are fixed based on the Cycle 1 Day 1 date and will not change due to dose interruptions or delays. Management of toxicities should be performed as detailed in Sections 6.3.1 and Section 6.3.2. Once the dose of study drug is reduced, any re-escalation to a full starting dose must be discussed in advance with the sponsor's medical monitor (with the exception of dose reduction for liver function test [LFT]-related toxicity, for which no dose re-escalation will be permitted, as discussed in Section 6.3.1.1).

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/placebo or AA.

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

6.3.1. Non-hematologic Toxicities

For subjects who develop drug-related Grade 3 or higher toxicities, treatment should be withheld unless appropriately managed per institutional standard. 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/placebo or AA only, then both niraparib/placebo 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. Subjects who are reported with treatment-related hypertensive crisis will have both study drugs (niraparib/placebo and AA) permanently discontinued.

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)/placebo (from 2 capsules to 1 capsule). Note that if a subject was on a reduced dose of niraparib/placebo (100mg daily), niraparib/placebo must be discontinued for non-hematologic niraparib/placebo-related Grade ≥3 toxicities lasting continuously for more than 28 days.
- 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.

6.3.1.1. Hepatic Toxicities

Hepatic toxicities are a known potential side effect of AAP and niraparib, but are more common with AAP treatment.[15,16] Table 2 provides dose recommendations for subjects who develop liver function test abnormalities during treatment with niraparib/placebo and AAP. During dose interruptions, LFTs should be monitored at least weekly. For Grade ≥2 LFT abnormalities, LFTs should be monitored at least weekly until Grade 1 or baseline. For subjects being retreated, serum transaminases should be monitored at a minimum of every 2 weeks for 3 months and monthly for the next 3 months and then follow Time and Events Schedule 1.

Table 2: Dose Modification Criteria for AST/ALT/Bilirubin Abnormalities for Niraparib/Placebo and Abiraterone Acetate Plus Prednisone

Toxicity Grade	Dose of Niraparib/Placebo	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 100 mg (1 capsule) 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.	Must be interrupted and discussed with medical monitor. If ALT is ≥20 x ULN, discontinue and do not re-treat with AA.	No change or consider tapering if AA discontinued.
AA=abiraterone acetate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal			

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.

6.3.1.2. Hypokalemia

Hypokalemia is a known side effect of AAP.[15] Niraparib/placebo 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.

6.3.1.3. Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES) is characterized clinically by headache, seizures, altered mental status, and visual loss and with imaging findings of white matter vasogenic edema, predominately affecting the posterior and parietal lobes of the brain. Subjects who develop neurological symptoms suggestive for PRES should be immediately referred for neurological assessment and intake of niraparib/placebo and AA should be interrupted. If diagnosis of PRES is confirmed, treatment with study drugs must be permanently discontinued.

6.3.2. Hematologic Toxicities

Hematologic toxicities are not a known side effect of AAP and treatment with AAP should generally be continued during niraparib/placebo dose interruptions/modifications.

Niraparib/placebo dose interruption/modification criteria for platelet and neutrophil counts will be based on the criteria outlined in Table 3. 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. For Grade ≥3 anemia, niraparib/placebo should be interrupted until resolution to Grade <3.

The site should contact the sponsor for discussion and consider discontinuation of niraparib/placebo if hematologic toxicity has not recovered to Grade 1 or baseline after prolonged period of dose interruption.

Subjects who receive a confirmed diagnosis of MDS/AML should discontinue niraparib.

Table 3: Niraparib/Placebo Dose Modification/Reductions for Platelet and Neutrophil Counts

Toxicity Grade	Dose of Niraparib/Placebo
Grade 1	No change, consider weekly monitoring.
Grade 2	At least weekly monitoring and consider interrupting until ≤Grade 1 or baseline and then resume at same dose with recommendation of weekly monitoring for 28 days after restart.
Grade ≥3	Interrupt until ≤Grade 1 or baseline, then: • Resume at 200 mg or 1 dose-level reduction (at the discretion of the investigator). • If subject was already on reduced dose at 100 mg, (because of non-hematologic toxicity), discuss with sponsor prior to resuming treatment. Weekly monitoring is required until resolution to Grade 1 or baseline. Weekly monitoring is recommended for 28 days after restarting dose.
Second occurrence Grade ≥3	Interrupt until ≤Grade 1 or baseline and restart at 1 dose-level reduction. Weekly monitoring is required until resolution to Grade 1 or baseline. Weekly monitoring is 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

Notes:

- For subjects with a platelet count ≤10,000 cells/µL, prophylactic platelet transfusion per guidelines may be considered. For subjects taking anti-coagulant or anti-platelet therapy, consider the risk/benefit of interrupting these drugs or prophylactic transfusion at an alternative threshold such as ≤20,000 cells/µL.
- 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 for Grade ≥3 AE deemed to be related to niraparib toxicity, interrupt study drug and restart at 1 dose-level reduction after resolution to Grade 1 or baseline. If the subject was previously dose-reduced for the same hematologic toxicity, discontinue niraparib/placebo.

6.3.3. Treatment Interruptions for Procedures

Both niraparib/placebo 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.

6.4. Treatment of Overdose

Overdose is addressed in the niraparib and AA IBs,[15,16] and in the prednisone product information as follows:

- Niraparib: There is no specific treatment in the event of niraparib overdose. Physicians should follow general supportive measures, interrupt niraparib, and treat symptomatically.
- AA: In the event of an overdose, interrupt AA, undertake general supportive measures including monitoring for arrhythmias and cardiac failure as well as assess liver functions.
- Prednisone: Treatment of acute overdose (ie, ingestion of large quantities of prednisone over a very short period of time) 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:

- Closely monitor the participant for AE/SAEs and laboratory abnormalities and record in the eCRF. In the event an AE/SAE or laboratory abnormality is observed, continue monitoring until resolution or return to baseline.
- Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.
- Contact the Medical Monitor prior to re-starting study drug.

7. INTERVENTION COMPLIANCE

A count of all study drugs provided by the sponsor will be conducted during the Treatment Phase of this study. Study drugs will be dispensed, and dosing compliance will be assessed at study visits as described in Time and Events Schedule 1. If there are recurrent issues with dosing compliance in the absence of toxicity, the investigator or designated study-site personnel should re-instruct subjects regarding proper dosing procedures.

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (subject-by-subject accounting), and accounts of any study drug accidentally or deliberately destroyed. The amount of study 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).

8. CONCOMITANT THERAPY

Concomitant therapies must be recorded throughout the study beginning from screening up to 30 days after the last dose of both study drugs, unless the subject received new anti-prostate cancer treatment, has died, is lost to follow-up, or withdraws consent. In addition, all prestudy therapies administered up to 28 days prior to the first dose of study drugs must be recorded at screening. All therapies different from the study drugs must 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 required 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.

8.1. Prohibited Concomitant Medications

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which the following prohibited therapies are administered. If the permissibility of a specific drug/treatment is in question, please contact the sponsor.

- Investigational agents other than the study drugs
- Other anticancer therapies
- Other agents that target the androgen axis (eg, antiandrogens such as enzalutamide and apalutamide, or CYP17 inhibitors such as ketoconazole)

- Testosterone
- Radiotherapy for tumor progression. May receive palliative radiotherapy in selected cases after discussion with sponsor.
- Chemotherapy
- Immunotherapy
- Diethylstilbestrol (DES) or similar estrogen receptor agonists
- Pomegranates and pomegranate juice
- Spironolactone
- Radiopharmaceuticals such as radium-223 (^{223}Ra), strontium (^{89}Sr), or samarium (^{153}Sm)
- Strong inducers of CYP3A4 (eg, rifampin)

8.2. Restricted Concomitant Medications

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.[15,16] Additional information is provided in Attachment 2.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules summarize the frequency and timing of assessments applicable to this study. If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: Patient-reported outcomes (PRO) questionnaires first (to prevent influencing subject perceptions), ECGs, vital signs, and any type of blood draw last. Blood collections for PK assessments should be performed in the specified time windows as much as possible. 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 maximum amount of blood drawn should not exceed 60 mL at any visit. Refer to the laboratory manual for details regarding blood volumes to be collected for each visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Prescreening Phase for Biomarker Evaluation

During the Prescreening Phase, subjects will be evaluated for HRR gene alteration status (see Section 9.4 for definition of biomarker-positivity) and must meet the criteria described in Section 4.1. All subjects will be required to sign an ICF.

After signing the ICF, all subjects must have blood and tumor tissue (archival or recently collected) samples collected. HRR gene alteration status must be determined using the sponsor's required assays. However, if previous other local testing (by CLIA -certified or equivalent laboratory) shows a pathogenic germline or somatic HRR gene alteration (see Table 4, Section 9.5), then a subject may enter screening and be randomized (if eligible). If the subject has had sample previously analyzed by the sponsor's required assays, then after the subject grants a release, the data can be reviewed for biomarker status. Cohort assignment will be determined based on HRR gene alteration status as detailed in Section 9.4. Screening should occur within 6 weeks of receiving a final HRR gene alteration result from the sponsor.

For tumor tissue collection, either archival or recently collected tissue is acceptable. If no tumor tissue is available, then the subject may agree to have a new tumor tissue sample collected. If the sample (plasma or tissue) used to determine eligibility fails to produce a conclusive result, then another sample may be assessed.

SAEs related to the blood and tumor collection procedures will be collected from the time the ICF is signed until 30 days after the procedure occurs (see Section 12.3.1).

9.1.3. Screening Phase

During screening, eligibility criteria will be reviewed, and a complete clinical evaluation will be performed as specified in the Time and Events Schedules. Screening procedures may be performed up to 28 days prior to randomization, unless otherwise specified. Screening clinical safety laboratory evaluations (detailed in Section 9.7) may be used for Cycle 1 Day 1 assessments if performed within 14 days of Cycle 1. 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 randomization.

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 but requires sponsor approval

and agreement. After discussion with the sponsor, rescreened subjects may be able to use the initial screening laboratory results as long as safety laboratory evaluations (hematology panel, serum chemistry panel, and liver function tests) described in Section 9.7 have been performed within 14 days of randomization. Initial CT/MRI and bone scans may be used to determine eligibility if within 6 weeks of planned randomization. All other rescreening and subsequent randomization activities must be conducted in accordance with all protocol defined windows and timelines. The sponsor or designee will review results from the screening visit prior to randomization to confirm subject selection for the study.

For subjects who received AAP for mCRPC prior to study entry, the following conditions apply:

- If less than 2 months of AAP was administered at the time of randomization, then no additional investigations are required. These subjects may enter the study, if eligible by all other criteria.
- If ≥2 months, but ≤4 months of AAP was administered at the time of randomization, then at least 2 PSA values are required. The first PSA value should be available from approximately the time of AAP initiation, while the second PSA value should be obtained within 2 weeks of randomization. If PSA rise is observed and is considered by the investigator to be due to flare, then the investigator should confirm that there is no radiographic progression. If disease progression is confirmed by either PSA or radiographically, then the subject is not eligible as per Exclusion Criterion 3.1.
- If more than 4 months of AAP was administered, then the subject is not eligible as per Exclusion Criterion 2.1.

9.1.4. Treatment Phase

Treatment for Cohorts 1 and 2 will be double-blinded, while treatment for Cohort 3 (FDC) will be open-label. The Treatment Phase will begin at Cycle 1 Day 1 and will continue until both study drugs are discontinued. Subjects must start study drugs within 72 hours or 3 calendar days after randomization. The last measurements taken on Day 1 of Cycle 1 before administration of the study drugs or at screening (whichever value was last) will be defined as the baseline values. Visits for each cycle will have a ±3-day window, unless otherwise specified. Study visits will be calculated from the Cycle 1 Day 1 date, irrespective of any treatment interruptions. Subjects may have imaging performed within ±7 days of visits requiring images. Refer to the Time and Events Schedules for treatment visits and assessments during the Treatment Phase. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. Any on-study surgical procedures should be captured on the Surgical Procedures form in the eCRF. Study drug treatment will continue until unequivocal disease progression, unacceptable toxicity, death, or the sponsor terminates the study (see Section 10).

9.1.5. Futility Analysis for Cohort 2

As described in Sections 3.1.2 and 11.11, a non-binding futility analysis was performed for Cohort 2 after approximately 200 subjects were enrolled and approximately 125 progression events had occurred in this cohort. Futility was met for Cohort 2; therefore, no additional subjects will be enrolled in this cohort. Details regarding further treatment and data collection for these subjects is in Attachment 7.

9.1.6. End-of-Treatment Visit

An EoT visit should be scheduled within 30 days after the last dose of both study drugs 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, up to 30 days after the last dose of study drugs, unless the subject received new anti-prostate cancer treatment, 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.

9.1.7. Follow-up Phase

Once a subject has completed the Treatment Phase for a reason other than radiographic progression, CT/MRI, and bone scans (^{99m}Tc) should be collected every 3 months (±4 weeks) until confirmed radiographic progression or initiation of subsequent systemic therapy, provided the subject does not withdraw consent, is lost to follow-up, or dies. If a subject has documented radiographic progression during the Treatment Phase, additional radiographic assessments are not required during the Follow-up Phase.

After discontinuation of all study medications, subject status will be monitored every 3 months for up to 60 months (5 years) or until subject death, lost to follow-up, withdrawal of consent, or study termination. Information regarding survival status and initiation of subsequent prostate cancer therapies, as well as disease progression status on the subsequent therapies will be collected.

For the secondary and other endpoints, pain score (ie, Item #3 of the BPI-SF), subsequent therapy, radiation, cancer related procedures, symptomatic progression, and morbid events will continue to be collected as specified in Time and Events Schedules 1 and 3. Visits to the clinic are not required; sites may collect the information by telephone interview, chart review, or other convenient methods. 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.

During the Follow-up 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.

9.1.8. Extension Phase

Subjects will enter an Extension Phase (long-term or open-label) depending on their cohort assignment, after notification by sponsor letter.

Based on sponsor decision or in consultation with the IDMC, the sponsor will notify sites of timing and assignment of which Extension Phase to enter per cohort or subgroup of a cohort. Cohort 1

subjects and Cohort 2 subjects who were not included in the futility analysis are expected to enter either the OLE (Attachment 5) or the LTE (Attachment 6).

Cohort 3 subjects will enter the LTE (Attachment 6) after notification from the sponsor.

9.1.9. Evaluations

Efficacy evaluations will be conducted as specified in Time and Events Schedule 1. Unscheduled assessments should be considered if clinically indicated, and results collected in the eCRF. All imaging scans will be collected centrally to permit independent centralized review of blinded radiographic data.

9.1.9.1. Evaluations for Primary Endpoint

The primary endpoint for this study is rPFS as assessed by blinded independent central review (BICR), which will be evaluated using chest, abdomen, and pelvis CT or MRI scans and whole-body bone scans (^{99m}Tc). PET or PET CT scans cannot be used in place of technetium bone scan, conventional CT, or MRI. The same imaging modality should be used throughout the evaluation of an individual subject, if possible. Scans will be submitted and reviewed by a central vendor. Investigator assessed rPFS will be based on data collected in the imaging assessment eCRF forms. The radiographic progression date will be derived from these forms. Note that investigators should use BICR of imaging data to inform on decisions regarding treatment discontinuation for radiographic progression. Subjects without radiographic progression or death will be censored at the last disease assessment. Additional details are provided in Section 11.3.

9.1.9.2. Evaluations for Other Efficacy and Patient-reported Outcome Endpoints

Other efficacy evaluations include the following:

- Serum PSA (measurements at a central laboratory) evaluated by Prostate Cancer Working Group 3 (PCWG3) criteria[32]
- Survival status
- Subsequent systemic therapy for prostate cancer
- Cancer-related radiation therapy or surgical procedures
- Symptomatic progression
- PROs (see Section 9.5)

9.1.10. Criteria for Primary Endpoint

Radiographic progression should be evaluated as follows:

- Progression of soft tissue lesions measured by CT or MRI as defined in RECIST 1.1.[10]
- Progression by bone lesions observed by bone scan and based on PCWG3.[32] 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 baseline 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 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. The Week 8 scan will be considered as the baseline scan to which subsequent scans are compared. The FIRST scan timepoint that shows ≥2 new lesions compared with the Week 8 scan will be considered as the bone scan progression timepoint if these new lesions are confirmed by a subsequent scan ≥6 weeks later.
2. For a subject whose Week 8 scan does not have ≥2 new bone lesions compared to baseline scan, the FIRST scan timepoint that shows ≥2 new lesions compared with the Week 8 scan will be considered as the bone scan progression timepoint if these new lesions are confirmed by a subsequent scan ≥6 weeks later.

Evaluation of rPFS will be assessed by BICR as detailed in the Imaging Manual. Details regarding materials to be forwarded for central assessment can also be found in the Imaging Manual and/or Investigator Site File.

9.2. Pharmacokinetics

9.2.1. Sample Collection and Handling

Blood samples for PK analysis should be collected as specified in Time and Events Schedule 2. If a subject's study drug is interrupted (eg, for toxicity), the site should contact the sponsor for instructions regarding PK sample collection. Blood samples to measure plasma levels of niraparib and its metabolite, M1 (if judged relevant), will be obtained on Day 1 of Cycles 2 through 7. Other metabolite(s) of niraparib may also be measured in collected PK samples. Blood samples to measure plasma levels of abiraterone will be obtained on Day 1 of Cycles 2 and 3. Genetic analyses will not be performed on these samples. Subject confidentiality will be maintained.

The date and time of the PK samples and of the dose administered on all PK visit days and prior dose taken at home should be recorded. Refer to the laboratory manual for sample collection requirements, shipping instructions, and specified controlled temperatures for storage.

9.2.2. Analytical Procedures

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

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

9.2.3. Population Pharmacokinetic Parameters

Observed plasma concentrations of niraparib and M1 (if judged relevant) will be summarized by visit and timepoint. PK parameters will be derived using a population PK approach, as described in Section 11.4.

Abiraterone trough levels and descriptive statistics will be summarized by treatment and visit.

9.3. Pharmacokinetic/Pharmacodynamic Evaluations

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

9.4. Biomarkers

Subjects must have HRR gene alteration status assessed by the sponsor's required assays. If a previous result from the sponsor's required assays or local testing (by CLIA-certified or equivalent laboratory) shows a pathogenic germline or somatic HRR alteration for one of the selected genes, then after sponsor review of the results, the subject may enter screening and be randomized (if eligible). Blood and tumor tissue should be collected and submitted for all subjects. The biomarkers for this study are listed in Table 4. Cohort assignment will be performed by the sponsor, as detailed in Table 5.

While trial eligibility is based on HRR gene alteration status as defined in Table 4, additional data will be captured to determine biallelic HRR gene alteration status (eg, a homozygous deletion, or a genomic lesion required for positivity in combination with a deletion or loss of heterozygosity in the same gene). After the implementation of Protocol Amendment 3, enrollment of subjects with ATM alteration was stopped. The remaining enrollment for Cohort 1 may be further adjusted to include additional subjects with specific HRR gene alterations based on evidence from external data. These enrollment changes will be communicated to the investigators and sites through an investigator letter.

Table 4: Biomarker Panel and Criteria for Positivity

HRR Genes	Definition
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
CDK12	Cyclin-Dependent Kinase 12
FANCA	Fanconi Anemia Complementation Group A gene
PALB2	Partner and Localizer of BRCA2 gene
CHEK2	Checkpoint Kinase 2 gene
BRIP1	BRCA1 Interacting Protein C-terminal Helicase 1 gene
HDAC2	Histone Deacetylase 2 gene
ATM[1]	Ataxia Telangiectasia Mutated gene

HRR=homologous recombination repair

1. Subjects with ATM alterations were considered eligible for Cohort 1 prior to implementation of Protocol Amendment 3.

Table 5: Enrollment Assignments

Plasma Result	Tissue Result	Enrollment Assignment
HRR gene alteration positive	HRR gene alteration negative	Cohort 1
	HRR gene alteration positive	
	No reportable result	
HRR gene alteration negative	HRR gene alteration negative	Cohort 2
	HRR gene alteration positive	Cohort 1
	No reportable result	Cohort 2
Testing failure	HRR gene alteration negative	Cohort 2
	HRR gene alteration positive	Cohort 1
	No reportable result	Cohort 2

HRR=homologous recombination repair

Note: A subject with an HRR gene alteration positive result by either the sponsor's plasma or tissue assay can enter screening without waiting for results from the other assay. Subjects with a previous pathogenic HRR gene alteration by local testing will be permitted to enter screening; however, subjects should also have testing by the sponsor's assays.

Based on emerging scientific evidence, the sponsor may request additional blood samples for biomarker evaluation. In this case, such analyses will be limited to research related to the study drug(s) or diseases being investigated.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis 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 the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded 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.

9.4.1. Evaluations

Exploratory biomarkers (including CTC, DNA, and RNA) will be collected where local regulations allow. Any remaining samples may be used for future studies.

9.4.1.1. Circulating Tumor Cells

Blood samples should be collected at timepoints specified in Time and Events Schedule 1 for isolation of CTCs. CTC enumeration will be evaluated at the central laboratory, to assess response to treatment. CTCs will also be collected for molecular analysis. CTCs should be collected except where not permitted by local regulations or where required shipping and handling procedures cannot be executed.

9.4.1.1.1. Plasma for RNA

Plasma samples will be collected as specified in Time and Events Schedule 1 (at baseline and at progression) except where not permitted by local regulations. Multiple ribonucleic acid (RNA) transcripts found in prostate tumors are detectable in the plasma. The sample may be evaluated to understand potential mechanisms of resistance or response that may emerge with niraparib.

9.4.1.2. Plasma for DNA

Plasma samples will be collected as specified in Time and Events Schedule 1 (at baseline and during the course of treatment), except where not permitted by local regulations, and will be used to isolate circulating tumor DNA (ctDNA) from plasma. In addition, the cell pellet will be collected from Cycle 1 Day 1 to serve as a reference genome for sequencing analysis. Plasma isolated ctDNA may be evaluated for changes in the levels or types of DNA-repair anomalies observed over time, and to monitor for potential markers of resistance or response to niraparib and minimal residual disease. Plasma DNA from the biomarker panel for eligibility may also be used for potential bridging studies or for studies to further develop the diagnostic test to identify patients suitable for treatment with therapeutic regimens that include niraparib.

9.4.1.3. Tissue Analysis

Tumor tissue (either archival or recently collected) will be obtained to evaluate HRR gene alteration status and may also be used to identify markers associated with disease evolution, immune context, and response to study drugs. Furthermore, tumor tissue may be assessed for RNA signatures predictive of response to niraparib or AAP. Tumor tissue may also be used for potential

bridging studies or for studies to further develop the diagnostic test to identify patients suitable for treatment with therapeutic regimens that include niraparib.

9.5. Patient-reported Outcomes

The goal of collecting PRO data is to evaluate patient experience in terms of the benefit with regards to pain and prostate cancer symptoms, treatment-related tolerability or experiences, and overall health-related quality of life (HRQoL). Disease-related symptoms will be assessed using the BPI-SF and the prostate cancer symptom subscale of the FACT-P. Treatment-related tolerability and experiences will be assessed with selected items from the patient-reported version of the CTCAE, the PRO-CTCAE. These items will be analyzed along with the single item from the FACT-P regarding "side effect bother" to evaluate treatment-related tolerability to supplement the CTCAE report. Overall HRQoL will be measured with the FACT-P and the EQ-5D-5L to assess any impact to HRQoL from either disease-related or treatment-related experiences. The PRO collection schedule has been established to maximize utility through collections at timepoints most likely to capture a result and minimize subject burden by not collecting all PROs at each clinic visit. The PRO-CTCAE assessment is being piloted to gain experience with the use of this assessment for this patient population. Therefore, it will only be performed in the US and in English. PROs should be collected as per the timepoints in Time and Events Schedule 3.

All visit-specific PRO assessments should be conducted and completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. Detailed instructions for administering the PRO questionnaires will be provided in a PRO manual.

PRO measures will be administered to evaluate treatment-related tolerability, the delay of deterioration in symptoms, and HRQoL of niraparib and AAP compared to placebo and AAP.

Post-progression PRO data will be collected to understand the subject experience beyond progression. Therefore, during the Follow-up Phase, selected PROs can be completed either at the site or over the telephone as per the timepoints in Time and Events Schedule 3 for 2 years post end of treatment.

Efforts will be made to minimize and manage missing data to show a robust result (see Section 11.7). Sites will be proactively trained on how to assist subjects with PRO collection and sufficient time will be given to complete PROs. Electronic PRO information will also be monitored to evaluate for any trends in missing data so that investigative site staff can be retrained, if needed.

9.6. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study as specified in Time and Events Schedule 1. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct 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

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, ECOG PS, and other safety evaluations as described in Time and Events Schedule 1. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution, lost to follow-up, death, or until a clinically stable endpoint is reached.

Adverse Events

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

Clinical Laboratory Tests

Scheduled blood samples to assess the safety of the study drugs will typically be processed by a central laboratory. Local laboratory tests may be performed as necessary. 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: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade 1 or to baseline values.

Required laboratory tests must be performed within ±3 days of the scheduled visit during the Treatment Phase. In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

For any suspected MDS/AML case reported while a subject is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a hematologist. Testing completed as part of standard-of-care is sufficient. The study site must receive a copy of the hematologist’s report of aspirate/biopsy findings, and other sample

testing reports related to MDS/AML. Data from the report will be entered on the appropriate eCRF pages and the site must keep a copy of the report with the subject's study file.

The following tests will be performed as outlined in Time and Events Schedule 1 for Study Procedures/Assessments. Additional testing may be performed as clinically indicated after discussion with the medical monitor:

- Hematology Panel[a]

  -CBC (hemoglobin, total white blood cell count, platelets, absolute lymphocyte count, and ANC)[b]

- Serum Chemistry Panel[a]

  -creatinine
  -glucose
  -lactate dehydrogenase
  -potassium

- Liver Functions Tests[a,c]

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

- Other Laboratory Tests

  -testosterone[c]
  -serum albumin
  -PSA
  -serology (HIV and CD4 count if indicated, HBsAg, HepB core antibody, HCV antibody)[c]

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood cell count; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HepB=hepatitis B; HIV=human immunodeficiency virus; PSA=prostate-specific antigen

a. Safety labs which must be obtained within 14 days of randomization. Screening labs can be used if they are within this window.
b. CBCs should be performed weekly for the first cycle of treatment. LFTs should be performed every 2 weeks for the first 3 cycles of treatment.
c. Screening only. If Hepatitis B surface antigen and/or Hepatitis B core antibody are positive, additional testing with HBV DNA may be performed within the first cycle of treatment to evaluate the likelihood of hepatitis B reactivation in subjects with latent infection. If Hepatitis C antibody is positive and LFTs are abnormal, additional tests (eg, HCV RNA) may be performed within the first cycle of treatment.

Electrocardiogram (ECG)

ECGs (12-lead) will be recorded at screening (ie, within 28 days of randomization). Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the investigator. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. ECGs

should be obtained when serum potassium levels are within normal limits according to the most recent testing.

Vital Signs

Pulse/heart rate, and BP will be recorded at the timepoints outlined in Time and Events Schedule 1.

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 is required. Only clinically relevant abnormalities found on physical examination should be reported as AEs in the eCRF.

ECOG Performance Status

The ECOG PS scale (provided in Attachment 1) will be used to grade changes in the subject's daily living activities. The frequency of ECOG PS assessment is provided in Time and Events Schedule 1.

9.8. Sample Collection and Handling

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

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

10.1. Completion

A subject will be considered to have completed the Treatment Phase when a clinical endpoint is reached (death, radiographic progression or clinical progression per protocol definition, or unacceptable toxicity). All subjects will be followed for survival.

10.2. Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study after discontinuation of the study drugs. Subjects who discontinue the study treatment should complete the EoT visit within 30 days after both study drugs are discontinued and prior to administration of a new anti-prostate cancer therapy. Subjects ordinarily should be maintained on study treatment until confirmed radiographic progression. If the subject is found to have radiographic progression on the local radiology read and the investigator plans to discontinue study treatment, the site should submit the scan for central review, indicate that radiographic progression is suspected, and upload the local radiology read information into eDC. The subject should not be discontinued from study treatment until there is radiographic progression as per the central radiology review. If the subject has radiographic progression but not unequivocal clinical progression and alternate treatment is not initiated, the subject may continue on study treatment, at the investigator's discretion after discussion with the sponsor. After radiographic progression has been confirmed, subjects remaining on study treatment should undergo scans as per local standard of care. Study treatment should 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 study therapy.[30]

A subject's study treatment should be discontinued for study drug-related toxicity (as defined in Section 6.3) or unequivocal clinical progression. All efforts must be made for the subject to undergo radiologic assessment prior to discontinuing study treatment. Unequivocal clinical progression is defined as:

Deterioration in ECOG PS to Grade 3 or higher.

Need to initiate any of the following because of tumor progression:

- Alternative anticancer therapy for prostate cancer.
- Radiation therapy for tumor progression.
- Surgical interventions for complications due to tumor progression.

10.3. Withdrawal from the Study

A subject will be considered withdrawn from the 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
- 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, he will agree to be contacted periodically by

the investigator to assess endpoint status. 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. Subject's survival status may be obtained by public record or cancer registry where permitted by local regulations. Sites may be contacted in between scheduled follow up to collect survival in anticipation of database locks.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study 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 Samples in Future Research

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 efficacy and safety data is outlined below. Specific details will be provided in the SAP.

For the primary endpoint, subjects with BRCA1 or 2 gene alterations (the BRCA subgroup) of Cohort 1 will be analyzed first. If statistical significance is reached in the BRCA subgroup, then the entire population of subjects with HRR gene alterations (Cohort 1) will be tested. If rPFS in Cohort 1 is significant, then the secondary endpoints will be tested in Cohort 1 using a group sequential method with 2 interim analyses and a final analysis.

Given that futility was met in Cohort 2, the analyses in the full ITT population, inclusive of Cohort 1 and Cohort 2 are removed from all formal statistical assessments for efficacy.

11.1. Analysis Populations

The following analysis populations will be defined in this study:

Randomized Analysis Set for Cohort 1: Randomized subjects in Cohort 1 will be used for efficacy analysis for Cohort 1.

Safety Analysis Set: The safety analysis set includes all randomized subjects who received at least 1 dose of study medication in Cohort 1 and Cohort 2. The safety analysis set will be used for evaluating safety and treatment compliance. Safety analysis will be performed separately by Cohort.

FDC Analysis Set: All subjects who were enrolled into Cohort 3 will be used for baseline and demographic data analysis, and their clinical experience will be described. All subjects who received at least 1 dose of study medication in Cohort 3 will be evaluated for safety.

11.2. Sample Size Determination

Approximately 400 subjects with L1 mCRPC and HRR gene alterations in Cohort 1 will be randomized in a 1:1 ratio to receive niraparib and AAP or placebo and AAP. It is assumed that the primary endpoint of rPFS follows an exponential distribution with a constant hazard rate. It is estimated that approximately 220 rPFS events will be required to provide 87% power in detecting a hazard ratio (HR) of 0.65 (median rPFS of 13 months[29] for the placebo and AAP treatment arm versus 20 months for the niraparib and AAP treatment arm) at a 2-tailed level of significance of 0.05. With a 21-month accrual period and an additional 7 months of follow-up, the study duration to reach the required number of rPFS events will be approximately 28 months. Assuming approximately 50% of Cohort 1 are subjects with BRCA1 or 2 gene alterations (the BRCA subgroup), with the planned sample size and study duration, approximately 102 rPFS events will be observed to provide 93% power to detect a HR of 0.5 in the BRCA subgroup (median 13 versus 26 months) at a 2-tailed level of significance of 0.05. The BRCA subgroup is expected to be at least 50% of Cohort 1. Enrollment of subjects with particular gene alterations may be halted when sufficient numbers of a particular gene alteration have been enrolled.

The study was originally designed with a long-term survival follow-up until approximately CCI deaths would have been observed for the ITT population (Cohort 1 and Cohort 2 randomized subjects). Assuming a median survival of C months for the placebo and AAP arm, the study duration to observe CCI deaths will be approximately C months, at which time CCI deaths are expected in Cohort 1. With CCI deaths, the power to detect a HR of CCI in the ITT population with a 2-tailed significance level of CCI Given the outcome of the futility analysis for Cohort 2, the analysis of Cohort 1 will proceed as planned when approximately CCI death events are observed in Cohort 1.

After the IDMC reviewed the futility analysis results on 13 August 2020, Cohort 2 was considered futile and enrollment into Cohort 2 was halted. Therefore, the ITT Population (Cohort 1 and Cohort 2 randomized subjects) will no longer be analyzed for efficacy.

11.3. Efficacy Analyses

The final analysis of the primary endpoint rPFS will be performed when approximately 220 rPFS events are observed in Cohort 1 and approximately 102 rPFS events are observed in the BRCA subgroup within Cohort 1. Sensitivity analysis will be performed by including the 14 subjects with CDK12 alteration from Cohort 2 to Cohort 1 on primary and secondary endpoints.[21]

Efficacy analysis will begin by testing rPFS in the BRCA subgroup of Cohort 1 using a 2-sided alpha level of 0.05. If significance is met in the BRCA subgroup, then rPFS in all of Cohort 1 will be tested, also at a 2-sided alpha level of 0.05. If rPFS in Cohort 1 is significant, then the secondary endpoints will be tested using a group sequential method with 2 interim analyses and a final analysis. The SAP will provide details on the graphical testing approach that will be used to strictly control the family-wise type 1 error rate at 2-sided 0.05 level across rPFS and the secondary endpoints in Cohort 1.[21]

All continuous variables will be summarized using number of subjects (n), mean, standard deviation (sd), median, minimum, and maximum. Discrete variables will be summarized with number and percent. The Kaplan Meier product limit method and a stratified Cox model will be used to estimate the time-to-event variables and to obtain the HR along with the associated confidence intervals. Unless otherwise specified, stratified log-rank tests (see Section 5.1 for stratification variables) will be used to test the treatment effect for time-to-event variables; response rate variables will be evaluated using the chi square statistic or the exact test if the cell counts are small.

11.3.1. Endpoints

Primary Endpoint

The primary endpoint is rPFS, as assessed by the central review, and defined as the time from the date of randomization to the date of radiographic progression or death, whichever occurs first. Radiographic progression is defined in Section 9.1.10.

Secondary Endpoints

The secondary endpoints are defined as below (details in the SAP):

- OS: defined as the time from date of randomization to date of death from any cause.
- Time-to-symptomatic progression: defined as the need to initiate/record any of the following:

  The use of EBRT for skeletal symptoms.

  The need for tumor-related orthopedic surgical intervention

  Other cancer-related procedures (for example: nephrostomy insertion, bladder catheter insertion, EBRT, or surgery for tumor symptoms other than skeletal).

  Cancer-related morbid events (for example: fracture [symptomatic and/or pathologic, cord compression, urinary obstructive events).

  Initiation of a new systemic anti-cancer therapy because of cancer pain.
- Time-to-initiation of cytotoxic chemotherapy: defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer.

Other Endpoints

- Time-to-PSA progression according to PCWG3 criteria defined as the time from date of randomization to the first date of documented PSA progression based on PCWG3.[32]
- PFS2: defined as time from randomization to the date of first progression (radiographic, clinical, or PSA progression) on the first subsequent therapy or death from any cause, whichever occurs first.
- Time-to-pain progression: defined as the time from date of randomization to the date of the first observation of pain progression. Pain progression is defined as an increase by at least 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive evaluations.

11.4. Pharmacokinetic Analyses

Plasma concentrations for niraparib, M1 and abiraterone will be listed and summarized using descriptive statistics. Population PK analysis of plasma concentration-time data of niraparib will be performed using nonlinear mixed-effects modeling. Previously developed population PK model for niraparib will be used as prior information to obtain individual estimates of exposure. If deemed necessary, the plasma concentration data obtained in this study may be pooled with data from previous studies, used to develop the population PK model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) may be explored as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis may be presented as a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for niraparib or abiraterone. PK samples collected after the snapshot date may be halted if PK objectives have been met. 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 concentrations. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, 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.

Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individually derived PK parameters including exposure information of niraparib, its M1 metabolite (if applicable), and abiraterone.

11.5. Biomarker Analyses

The concordance of HRR gene alteration status between tumor DNA and plasma ctDNA will be evaluated. The concordance of biomarker-positivity prediction between tumor DNA, plasma ctDNA, and CTC phenotype and number may also be evaluated.

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

11.6. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between niraparib measures of exposure (eg, derived AUC or trough concentrations) and key efficacy (eg, rPFS) and safety parameters, will be explored graphically,

as data allow. In addition, the relationship may be characterized using an exposure-response or logistic regression model. Details will be provided in an analysis plan and detailed results may be reported separately from the CSR.

11.7. Patient-reported Outcomes Analyses

Established minimum clinically important differences (MCIDs) will be used for time-to-degradation and proportional analyses.[5,6] The MCIDs for this study, based on the PROs selected, are provided in Table 6. Note that the PRO-CTCAE will not be included in the MCID analysis as it is an exploratory assessment being conducted only in the US.

Table 6: Minimum Clinically Important Differences

PRO total score or domain	Threshold for definition of deterioration
	Scores increasing reflect a worsening/deterioration
Worst Pain (BPI Question #3)	Pain progression is defined as an average increase by 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive evaluations ≥3 weeks apart.
Pain Interference score (combination of BPI scale scores 9a through 9g)	≥ half standard deviation of baseline
Average pain (Average of BPI3-6)	≥30% of baseline
FACT-P	Scores decreasing is worsening/deterioration
Physical Well-Being (PWB)	≤3
Social/Family Well-Being (SFWB)	≤3
Emotional Well-Being (EWB)	≤3
Functional Well-Being (FWB)	≤3
FACT-G (General) Scale	≤9
Prostate Cancer Subscale (PCS)	≤3
Trial Outcome Index (TOI)	≤9
FACT-P Total Scale	≤10
FACT-P Pain Scale	≤2
FAPSI-8	≤3
EQ5D HUI	0.08
EQ VAS[26]	10

Missing data for PROs will be analyzed by accounting for change from baseline with a mixed model of repeated measures and using a pattern mixture model as a sensitivity analysis. Fixed effects for the models will include treatment and visit number as discrete parameters, and interaction between time and treatment; subject is included as random effect. In addition, as a sensitivity analysis, a pattern mixed model will be applied assuming PRO data is not missing at random.[18] Details of PRO analyses will be provided in the SAP.

11.8. Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by treatment group. Detailed analyses of medical resource utilization will be reported separately from the CSR.

11.9. Safety Analyses

Treatment-emergent AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the National Cancer Institute-Common

Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5. Treatment-emergent AEs are those events that occur or worsen on or after first dose of study drug through 30 days after the last dose of study drug and will be included in the analysis. AEs will be summarized by System Organ Class and Preferred Term 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 BP (systolic and diastolic) values and changes from baseline will be summarized. The percentage of subjects with clinically important changes from baseline will be summarized.

Physical Examination

Abnormal findings in physical examination will be recorded and summarized as AEs.

11.10. Interim Analysis

There are no interim analyses for the primary endpoint of rPFS. Two interim analyses and one final analysis for the secondary endpoints (TSP, TCC and OS) are planned when approximately CCI CCI and CCI OS events have been observed in Cohort 1, respectively. The first interim analysis (IA1) is approximated such that it will be performed at the time of rPFS final analysis for Cohort 1.

11.11. Futility Analysis

A futility analysis will be performed for a go/no-go decision after approximately 200 subjects are enrolled and approximately 125 progression events (PSA progression events or rPFS events, whichever occurred first) are observed in the no HRR gene alteration cohort (Cohort 2). Guided by pre-defined statistical criteria and based on time-to-PSA progression and rPFS, as well as the totality of all the data, the IDMC was to make a recommendation regarding whether the study will continue enrollment to the prespecified sample size of approximately 600 subjects or discontinue enrollment. The futility analysis is non-binding, and the final decision was made by the sponsor based on the IDMC recommendation, totality of the data, and other development considerations. The details of the go/no-go decision rule will be detailed in the SAP.

Futility was met for Cohort 2; therefore, no additional subjects will be enrolled in this cohort.

11.12. Independent Data Monitoring Committee

An IDMC will be commissioned to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study and to review efficacy information. The IDMC responsibilities, authorities, and procedures will be documented in a separate charter.

The IDMC will be composed of members not associated with the conduct of the study, except in their role on the IDMC. The sponsor will also designate an independent biostatistician not affiliated with the project to prepare and provide study data to the IDMC. Complete details regarding the composition and governance of the IDMC will be outlined in the IDMC Charter.

12. ADVERSE EVENT, SERIOUS ADVERSE EVENT, AND OTHER SAFETY 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.

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), with the exception of the Prescreening Phase, where only SAEs related to blood or tumor collection procedures are collected (see Section 12.3.1).

Serious Adverse Event

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Related

An AE that might be due to the use of the drug.

12.1.3. Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE (Version 5.0). Any AE not listed in the NCI-CTCAE will be graded according to the investigator’s clinical judgment using the standard grades as follows:

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

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

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4, Life-threatening: Urgent intervention indicated.

Grade 5, Death: Death.

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

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or 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)

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

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from screening until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. All related AEs should be followed until resolution. SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drugs, must be reported using the Serious Adverse Event Form. During the Prescreening Phase, only SAEs related to the blood or tumor collection procedures should be reported from the time the ICF is signed until 30 days after the procedure occurs. Prescreening Phase SAEs should only be reported to the sponsor’s pharmacovigilance team using the SAE forms and should not be entered in 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/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs, as well as PQCs, 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 email/fax. 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).

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

12.3.3. 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 Section 13.

12.3.5. Pregnancy

Niraparib has the potential to cause teratogenicity or embryo-fetal death because niraparib is genotoxic and targets actively dividing cells in animals and patients (eg, bone marrow). In animal studies, niraparib showed effects on sperm (reduced sperm count, spermatids, and germ cells in epididymites and testes). Based on animal studies, niraparib may impair fertility in males of reproductive potential. AA was not noted to be genotoxic in in vitro studies; however, abiraterone is contraindicated in women who are or may become pregnant.[15]

Pregnancies in partners of male subjects included in the study should be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Pregnant partners of male subjects should also be appraised of the potential risk to the fetus.

12.3.6. Disease Progression and Death

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

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 AEs (regardless of relationship to study drug) after screening should be reported as SAEs for subjects until 30 days after the last dose of both study drugs. Death is an outcome of an AE and not an AE itself. All reports of death due to an AE within 30 days of the last dose of both study drugs should include an AE term for the cause of death (if known). Fatal events occurring after that 30-day window 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 efficacy 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.

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.

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 Safety, Including Product Quality

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

14. STUDY DRUG INFORMATION

Refer to Attachment 4 for information on the FDC tablet formulation.

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.[15]
- Placebo for niraparib will be provided as a capsule formulation and will be matched in size, color, and shape to maintain the study blind. It will be manufactured and provided under the responsibility of the sponsor.
- The AA tablet supplied for this study contains 250 mg of AA. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.[15]
- Prednisone tablets containing 5 mg prednisone will be provided directly by the sponsor.

14.2. Packaging

Niraparib 100 mg capsules and AA 250 mg tablets will be packaged in high-density polyethylene bottles with child-resistant closures. Packaging for the niraparib placebo will be identical to the packaging for the active drug.

Prednisone will be packaged in blister packs or 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

Caregivers should handle niraparib with protection (eg, gloves). Niraparib may have adverse effects on a fetus in utero. AA is contraindicated in women who are or may potentially be pregnant. There are no human data on the use of AA in pregnancy. Women who are pregnant or may be pregnant should not handle AA without protection (eg, gloves).

It is not known whether niraparib is present in or has transient effects on the composition of semen or whether abiraterone or its metabolites are present in semen. Therefore, to avoid risk of drug exposure for either study drug through the ejaculate (even men with vasectomies), subjects must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed while on study drug and for 3 months following the last dose of study drug. Refer to the IB, 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. Study-site personnel will instruct subjects on how to store study drugs for at-home use as indicated for this protocol. Subjects should be advised to keep all medications out of reach and sight of children.

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.

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 Brochures for niraparib and AA
- Electronic data capture (eDC) manual
- Study-site investigational product and procedures manual
- IWRS manual
- Pharmacy manual
- Laboratory manual
- Sample ICF
- Tablet for on-site PRO collections
- PRO questionnaires and completion guides
- RECIST guidelines, version 1.1
- PCWG3 guidelines
- Subject wallet card

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a randomized, double-blind study to assess the efficacy, safety, and PK, 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 HRR gene alterations, outweighs the potential risks involved as described in Section 1.5.

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

All participating subjects will receive full supportive care and will be followed closely for efficacy and safety throughout the study. As rPFS is the primary end point, scheduled imaging is incorporated into the protocol. The timing of imaging is designed to evaluate response and capture progression events and allow the clinical investigator to make timely treatment decisions yet balancing this with preventing subject overexposure to radiation. The frequency of scanning is consistent with requirements to assess rPFS by PCWG3 criteria and has been utilized on other pivotal metastatic prostate cancer studies.[3,29,32] An IDMC will be commissioned to review the efficacy and safety of the treatment on an ongoing basis and make recommendations as to the future conduct of the study.

As with all clinical and PK studies, there are risks associated with venipuncture and multiple blood sample collection. The blood sample collection scheme was designed to collect the minimum number of blood samples that can determine the efficacy, safety, PK, and biomarker requirements of the study. 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.[36]

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.

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.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and

regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

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

Exploratory DNA, 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 AA, to understand prostate cancer in patients with DNA-repair anomalies, to understand differential drug responders, and to develop tests/assays related to niraparib and AA and prostate cancer in patients with DNA-repair anomalies. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (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 sub-investigators.
- Documentation of sub-investigator 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 randomized 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 efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; electronic PROs; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. In addition, the author of an entry in the source documents should be identifiable.

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

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

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

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system, but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

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

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The CRF 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 eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the 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.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may physically or virtually 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 AA 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 AA, 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. 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. If issues arise regarding scientific integrity or regulatory compliance, then 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 important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: 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 2: 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 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 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	
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, All Adverse Events. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) as per applicable clinical trial legislation to Health Authorities and IRB/ECs. If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting. To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/ECs. 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: Open-Label Fixed-Dose Combination- Cohort 3

1. SYNOPSIS

The sponsor is developing an FDC tablet formulation with each tablet composed of niraparib 100 mg and abiraterone acetate (AA) 500 mg. To evaluate the clinical experience of the FDC tablet formulation, a separate open-label cohort (Cohort 3) has been added to Study 64091742PCR3001. Enrollment of subjects into Cohort 3 may begin after enrollment into Cohort 1 (HRR gene alteration) and Cohort 2 (no HRR gene alteration) has completed or when the sponsor opens Cohort 3 for enrollment. Cohort 3 will enroll in countries where permitted by local regulations.

The intended dosing regimen in patients with mCRPC is 200 mg niraparib and 1,000 mg AA daily, which is the same dose as has been used in Cohorts 1 and 2 of this study where niraparib and AA are given as separate components. Subjects receiving the FDC will start with 2 FDC tablets orally once daily and 5 mg prednisone orally twice daily.

Up to approximately 100 subjects with HRR gene alterations (approximately half of whom should have BRCA alterations) may be enrolled into Cohort 3.

Cohort 3 will be enrolled under the same inclusion/exclusion criteria and undergo the same study procedures as Cohort 1, with the exception that subjects in Cohort 3 will receive open-label niraparib and AA as an FDC tablet formulation instead of as single agents. Cohort 3 will not be included as part of the ITT or Safety Population and will not be included in the primary analysis. Cohort 3 will be described separately as noted in Section 9 of this Attachment and described in the SAP.

2. BACKGROUND AND RATIONALE

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 from Study 64091742PCR1001, the single-agent 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 plus prednisone or prednisolone. Reducing the pill burden for patients with cancer receiving oral medications may improve compliance as cancer patients often take multiple oral medications for cancer and for other comorbid conditions.[14]

In Cohort 3, the sponsor will evaluate the clinical experience with the regular strength FDC tablet formulation in the same patient population as that in Cohorts 1 and 2. It is expected that the FDC tablet formulation (2 tablets each containing100 mg niraparib/500 mg AA) would result in similar safety and efficacy as the single-agent combination.

The sponsor is also developing a low-strength FDC tablet formulation to allow for dosing modifications. The low-strength FDC tablet formulation has 50 mg niraparib and 500 mg AA per

tablet. 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, anemia, thrombocytopenia, neutropenia). Based on data from Study 64091742PCR1001, in the niraparib and AAP treatment group, 21% of subjects with a starting niraparib dose of 200 mg had a dose reduction of niraparib to 100 mg, most frequently due to cytopenias, and only 5% had a dose reduction of 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. If the low-strength FDC tablet is not available for the study, or if the prescribed dose cannot be achieved with the low-strength FDC tablet, then single-agent treatment will be supplied.

The benefit-risk profile for the niraparib/AA FDC tablet is expected to be largely the same as for niraparib and AA administered as single agents (Section 1.5 of the protocol) with the additional benefit of a decreased pill burden, and the excipients used are similar.

3. OBJECTIVES

The primary objective of Cohort 3 is to describe the clinical experience with niraparib and AAP administered as FDC tablets of niraparib and AA, plus prednisone. See Section 9 below for a description of planned analyses; full details are in the SAP.

4. STUDY DESIGN

Cohort 3 is a non-randomized, open-label treatment group. Up to approximately 100 subjects may be enrolled (see details in Section 5 below) and will receive niraparib and AA as an FDC tablet plus prednisone. Study procedures for Cohort 3 are the same as those for Cohorts 1, with the exception of study medication/dose modification, treatment allocation, and statistical analysis. Procedures specific to Cohort 3 are outlined below; otherwise, procedures should be followed per protocol.

5. SUBJECT POPULATION: SEE SECTION 4 OF THE PROTOCOL

The prescreening, inclusion, and exclusion criteria for Cohort 3 are the same as for Cohort 1. Up to approximately 100 subjects with HRR gene alterations (approximately half of whom should have BRCA alterations) may be enrolled into Cohort 3. The sponsor may adjust the number of subjects with specific HRR gene alterations. See the SAP for further detailed sample size information.

6. TREATMENT ALLOCATION AND BLINDING: SEE SECTION 5 OF THE PROTOCOL

Procedures for entering subject information into IWRS and for biomarker assessment apply for Cohort 3. However, subjects in Cohort 3 will not be randomized and treatment will not be blinded. All subjects will receive the niraparib and AA FDC tablets plus prednisone, unless otherwise specified per Section 7 of this Attachment.

7. DOSAGE AND ADMINISTRATION: SEE SECTION 6 OF THE PROTOCOL

7.1 Study Drug Administration for Cohort 3

Enrollment into Cohort 3 and administration of the FDC treatment regimen will be undertaken only following full approval of protocol amendment 4 from the HA and IEC/IRB (as applicable) at a site, completion of enrollment into Cohorts 1 and 2, or when the sponsor opens this cohort for enrollment.

Subjects in Cohort 3 will receive open-label study drug as regular strength niraparib/AA FDC tablets containing 100 mg niraparib/500 mg AA per tablet. Niraparib/AA FDC will be provided to subjects as 2 tablets comprising a total dose of 200 mg niraparib and 1,000 mg AA for once daily oral administration under modified fasting conditions. Prednisone will be provided as 5mg tablets for twice daily oral administration (total daily dose of 10 mg).

Subjects on the FDC treatment regimen who require dose modifications due to toxicities, will receive the low-strength FDC tablet when available (see Section 7.2 below). If the low-strength FDC tablet is not available, or if the prescribed dose cannot be achieved with the low-strength FDC tablet, then single-agent treatment will be supplied.

For dose interruptions/reductions for subjects receiving the FDC treatment regimen, see Section 7.2 below.

7.2 Dose Modification and Management of Toxicities with Niraparib/ Abiraterone Acetate Fixed-dose Combination

Dose reductions of niraparib can be achieved by using single--agent products (1 capsule of niraparib 100 mg and 4 tablets of AA 250 mg [total dose 1,000 mg]) or, as available, by using 2 x50-mg niraparib/500-mg AA FDC tablets (total dose 100 mg niraparib/1,000 mg AA). The dose reduction guidelines for subjects treated with the FDC are outlined in Table 7.

Dose modification instructions for single-agent niraparib and AA are in Section 6.3 of the protocol.

Table 7: Dose Reduction Guidelines for Subjects on the Fixed-Dose Combination Treatment Regimen

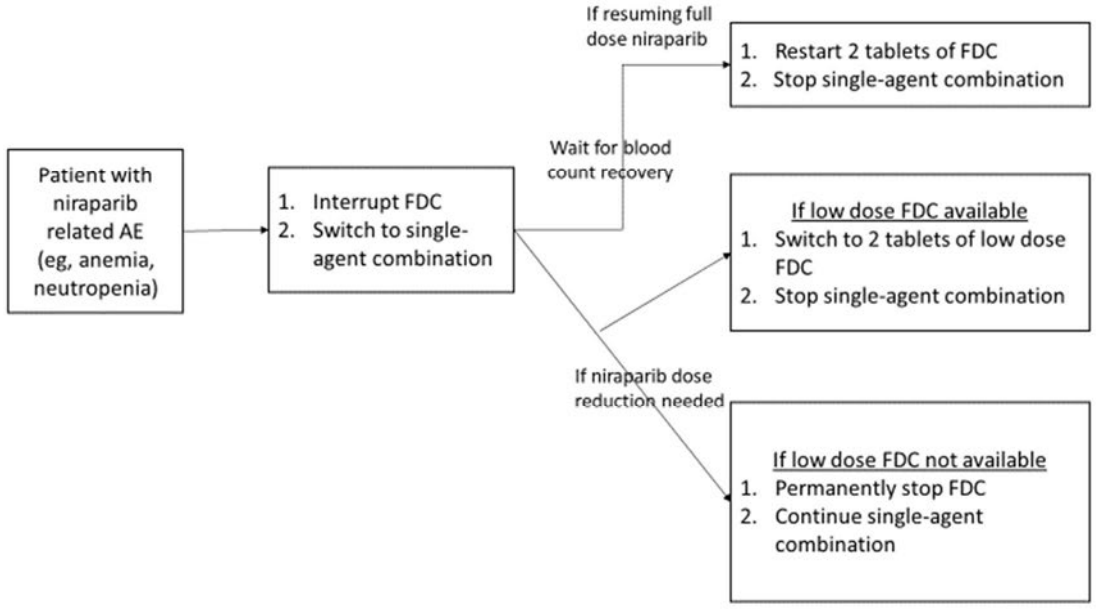
Dose Required	Dose of Niraparib	Dose of Abiraterone Acetate	Instruction
Reduced niraparib	100 mg	1,000 mg	Subjects will receive low-strength niraparib FDC tablets, if available; otherwise they will receive a single-agent combination of AA and niraparib
Reduced AA	200 mg (or 100 mg)	250-750 mg	Subjects will receive a single-agent combination of AA and niraparib
AA only	NA	500-1,000 mg	Subjects will receive single-agent AA. To restart niraparib as above.

AA = abiraterone acetate; eCRF = electronic case report form; FDC = fixed-dose combination.
Notes:

- Subjects diverted to the single-agent combination will receive AA as 250 mg tablets.
- Please contact the study team for further guidance and questions regarding study drug availability.
- All dosing information must be recorded in the eCRF.
- Low-strength FDC tablets contain 50 mg niraparib/500 mg AA

For management of hematologic toxicities, when the FDC treatment regimen needs to be temporarily interrupted, subjects should be switched to single-agent AA in combination with prednisone. A schematic overview of the FDC dose modification guidelines for management of hematologic toxicities are presented in Figure 3.

Figure 3: Dosing Modification Guidelines for Management of Hematologic Toxicities- Cohort 3: Fixed-dose Combination Regimen



AA = abiraterone acetate; AE=adverse event; eCRF=electronic case report form; FDC = fixed-dose combination.
Notes:

- Study drugs:
  - Single-agent combination: niraparib 100-mg capsules and AA 250 mg tablets.
  - Regular-strength FDC tablets: 100 mg niraparib/500 mg AA.
  - Low-strength FDC tablets: 50 mg niraparib/500 mg AA.
  - Prednisone, at the prescribed dose, should be continued as long as AA is administered.
- All dosing information must be recorded in the eCRF.

8. STUDY EVALUATIONS: SEE SECTION 9 OF THE PROTOCOL

All study evaluations are per protocol, except as noted below.

- Open-label treatment will begin at Cycle 1 Day 1 and will continue until both drugs are discontinued.
- Futility was met for Cohort 2, therefore, only subjects with HRR gene alterations will be enrolled into Cohort 3.
- Where mentioned in Section 9.1.4 of the protocol, “Blinded Treatment” is replaced with “Open-label Treatment” for Cohort 3.

9. STATISTICAL CONSIDERATIONS AND ANALYSES

The goal of this cohort is to collect clinical experience data for the FDC formulation. Primary and secondary endpoints along with safety data will be described separately for this cohort, and details will be provided in the SAP.

10. STUDY DRUG INFORMATION

10.1 Physical Description of Study Drugs

- Niraparib/AA FDC tablets (compound designation CJNJ-67652000) will be manufactured and provided under the responsibility of the sponsor.
- The FDC drug product formulations will be manufactured as immediate-release film-coated 100 mg niraparib/500 mg AA (regular-strength) and 50 mg niraparib/500 mg AA (low strength) tablets for oral administration containing 159.40 or 79.70 mg of niraparib tosylate monohydrate drug substance, respectively, equivalent to 100 or 50 mg niraparib free base, and 500 mg of AA drug substance. Refer to the Pharmacy Manual for a list of excipients.

A description of the niraparib and AA single agents and prednisone is in protocol Section 14.1.

10.2 Packaging

Niraparib/AA FDC tablets will be packaged in high-density polyethylene bottles with child-resistant closures.

A description of the packaging for niraparib and AA single agents and prednisone is in protocol Section 14.2.

10.3 Preparation, Handling, and Storage

Caregivers should handle niraparib/AA FDC tablets with gloves.

See protocol Section 14.4 for preparation, handling, and storage information for niraparib and AA single agents and prednisone.

Attachment 5: Open-Label Extension Phase

In the event of a decision to allow subjects to cross over from placebo to active drug, the Open-label Extension (OLE) Phase may be initiated for Cohort 1 subjects and Cohort 2 subjects not included in the futility analysis. The purpose of this phase is to provide treatment to subjects, while minimizing data collection burden. This phase will begin when both Amendment 5 is approved at the site and upon notification from the sponsor to the site to initiate the OLE.

- Cohort 1 subjects who were randomized to receive niraparib + AAP and are still on study treatment will be offered the option to continue to receive open-label niraparib + AAP until they reach a reason for discontinuation of treatment (see protocol Section 10.2) or until further notification by the sponsor of a different means for continued supply of study treatment, whichever occurs first.
- For subjects randomized to receive placebo +AAP and still on study treatment, the investigator may choose to cross the subject over to start receiving open-label niraparib + AAP if the subject meets the eligibility criteria below. Investigators can also choose to maintain the subject on AAP alone in which case eligibility criteria below do not need to be evaluated.
- Subjects who discontinued AAP due to an AE may receive single--agent niraparib.
- Subjects who discontinued niraparib/placebo due to an AE may continue to receive AAP.
- Subjects who have already ended study treatment altogether and are in the Follow-up Phase in the main study may not return to study treatment and will only have survival information collected.

The End-of-Treatment Visit for the Double-blind Treatment Phase should occur within 3 months of the Amendment 5 approval date at the site, or when the sponsor's decision is made to allow the study to proceed into the OLE, whichever date is later.

Eligibility Criteria for Subjects who Cross-over to Open-label Niraparib after Unblinding

Subjects from Cohort 1 who are identified as candidates for cross-over to open-label niraparib should meet the eligibility criteria below within 28 days prior to initiating open-label niraparib. Re-evaluation of out-of-range criteria may be permitted after discussion with the sponsor. If a subject does not meet these criteria, he can continue AAP alone.

1. Still participating in the Treatment Phase of the study
2. Willing and able to provide informed consent to receive open-label niraparib
3. ECOG PS grade of 0 or 1 (see Attachment 1)
4. Adequate organ function as defined by the following (both local and central labs are permitted):
   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
   b. Hemoglobin ≥9.0 g/dL, independent of transfusions for at least 30 days.
   c. Platelet count $\geq 100 \times 10^9$/L.
   d. Serum albumin ≥3.0 g/dL.

e. Creatinine clearance ≥30 mL/min 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 bilirubin and if ≤1.5 x ULN, subject may be eligible after discussion with the sponsor).

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

Study Treatment Administration

Androgen deprivation therapy (ADT) administration

ADT should be continued as per local practice.

Open-label study treatment

Study treatment taken orally on an outpatient basis and a treatment cycle is defined as 28 days (Table 8). Sufficient study drug for each treatment cycle will be distributed as specified in Table 9. Dose modifications for toxicity are provided in Section 6.3 of the protocol. Guidance for niraparib/placebo applies to open-label niraparib.

If a subject was on a lower dose of niraparib or AAP in the Treatment Phase of the study, he should continue on that lower dose in the OLE.

Table 8: Study Treatment Administration for the Open-Label Extension Phase

Study Treatments	Daily Dose	Schedule
niraparib	200 mg (2×100 mg capsules)	Once daily in the morning on an empty stomach. No food should be consumed for at least 2 hours before and at least 1 hour after dosing. Swallow capsules/tablets whole with water.
abiraterone acetate (AA)	1,000 mg (4×250 mg tablets)	
Prednisone	10 mg (2×5 mg tablets)	5 mg twice daily at any time (recommended to be taken with food)

If a subject forgets to take the study drugs at the regular time (ie, niraparib or AAP), then the missed dose(s) should only be replaced within the same day.

Prohibitions and Restrictions

Refer to protocol Sections 4.4, 8.1 and 8.2.

Study Procedures for the Open-label Extension

Subjects who meet the eligibility criteria will cross-over to open-label niraparib treatment beginning with Cycle X+1, where X is the last cycle the subject completed during the double-blind treatment phase.
All subjects continuing in the OLE should follow the schedule of procedures provided in Table 9.

Blood samples for serum chemistry and hematology should be collected from a local laboratory as specified in Table 9. The investigator should review the laboratory report, document this review, and record any clinically relevant changes in the AE section of the eCRF. For example, laboratory abnormalities leading to an action regarding study drug (dose change, temporary stop, delay of the start of a cycle, or permanent stop) or the start of concomitant therapy should be reported.

In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required.

After notification by the sponsor, subjects in OLE may be moved to long-term extension (Attachment 6).

Table 9: Time and Events Schedule (Open-Label Extension for Cohort 1)

Procedures	Notes	Subjects who Cross-over to Open-label Niraparib and AAP (ie, receiving niraparib for first time)	Subjects Remaining on Previously Received Study Treatment	Subjects off Study Treatment
Visit window during the Open Label Extension Phase is ±1 week.				
Screening				
Informed consent for the OLE Phase		X	X	
Eligibility		X		
Study Drug Dispensing				
Open label niraparib+AAP (or AAP alone)		Continuous; sufficient study drug until next visit will be dispensed		
Study drug compliance		Bottle(s) including any unused medication will be returned at every visit		
Visit Frequency				
Subject should visit the site		On D1 of OLE cycles 1 to 12, and then every 3 cycles.	On D1 of every 3 cycles	
Clinical Laboratory				
Safety Labs[a]	See Footnote a for required laboratory tests.	On D1 of each cycle until Cycle 12 of OLE, and then every 3 cycles (CBC weekly for the first cycle)	On D1 of every 3 cycles	
Safety				
Physical examination		At each visit. Clinically relevant abnormalities should be reported as AEs.		
BP Measurement		Weekly for 8 weeks[b] and then at each visit	At each visit	
ECOG		At each visit		
AE/SAE		X[c]		X[c]
Survival	May be obtained by telephone or chart review	X		X[d]
Efficacy				
Tumor assessments, PSA	As per local practice			

AAP abiraterone acetate plus prednisone or prednisolone; AE adverse event; C cycle; CCO FA clinical cutoff for final analysis; D day; EOT End of Treatment; ICF informed consent form; IWRS interactive web response system; OLE Open label Extension; PD progressive disease; PSA prostate specific antigen; SAE serious adverse event.

a. Hematology Panel: hemoglobin, WBC count, platelet count, and ANC, Serum chemistry panel: potassium, creatinine, Liver function tests: AST, ALT, and total bilirubin

b. During cycles 1 and 2 of the OLE, blood pressure monitoring should occur weekly beginning on C1D1. Blood pressure monitoring can occur at clinic visit or can be reported to the site by the subject, by home nurse, or by other method deemed reliable by the investigator.
c. Continuous during this period and until 30 days after the last dose if discontinued during this period. During follow up, SAEs thought to be related to study drug will be collected and reported via the SAE form within 24 hr of notification of the event.
d. Every 4 months until notified by the sponsor to stop collection. This includes subjects who come off of study treatment prior to entering the OLE Phase.

Note: The last visit of the Treatment Phase can be considered as the EOT visit

Attachment 6: Long-Term Extension Phase

The Long-term Extension (LTE) Phase will be initiated when both Amendment 5 is approved at the site and upon notification from the sponsor to the site to start LTE for a particular cohort or subset of a cohort of subjects. The purpose of this phase is to provide treatment to subjects, while minimizing data collection burden. Subjects entering LTE will continue to receive the study therapy that they were receiving at the time of transition to LTE. Investigators should monitor and assess the subjects for response, safety, and disease progression according to routine practice and local label requirements. Timing of assessments is at the discretion of the investigator. Data collection will be limited to SAEs, which will be reported on the SAE form up to 30 days after the last dose of study drug as specified in Section 12.3. No other safety nor any efficacy data are to be collected during the LTE; no analyses are planned for the LTE.

Subjects who had discontinued study treatment and are in the Follow-up Phase will be discontinued from the study upon the start of the LTE.

The sponsor will continue to provide study drugs until subjects reach a reason for discontinuation of treatment (see protocol Section 10.2) or until notification by the sponsor of a different means for continued supply of study treatment, whichever occurs first.

Study Treatment Administration

ADT administration

ADT should be continued as per local practice.

Open-label study treatment

Study treatment will be taken orally on an outpatient basis and a treatment cycle is defined as 28 days (Table 10). Sufficient study drug for each treatment cycle will be distributed as specified in Table 11. Dose modifications for toxicity are provided in Section 6.3 of the protocol. Guidance for niraparib/placebo applies to open-label niraparib.

If a subject was on a lower dose of niraparib or AAP in the Treatment Phase of the study, he should continue on that lower dose in the LTE.

Table 10: Study Treatment Administration for the Long-term Extension Phase		
Study Treatments	**Daily Dose**	**Schedule**
niraparib	200 mg (2×100 mg capsules)	Once daily in the morning on an empty stomach. No food should be consumed for at least 2 hours before and at least 1 hour after dosing. Swallow capsules/tablets whole with water.
abiraterone acetate (AA)	1,000 mg (4×250 mg tablets)	
Niraparib/Abiraterone acetate combination tablet	200mg/1000mg (2 combination tablets)	
Prednisone	10 mg (2×5 mg tablets)	5 mg twice daily (recommended to be taken with food)

Note: A patient who is continuing niraparib in combination with AAP may receive niraparib and AA either as single agents (ie, niraparib 100 mg capsules along with AA 250 mg tablets) or the FDC formulation (niraparib/AA 200mg/1000mg tablets) but not both.

If a subject forgets to take the study drugs at the regular time (eg, niraparib or AAP), the missed dose(s) should only be replaced within the same day.

Prohibitions and Restrictions

Refer to protocol Sections 4.4, Section 8.1 and Section 8.2.

Study Procedures for the Long-term Extension

All subjects continuing in the LTE will follow the schedule of procedures provided in Table 11.

Sites should follow the subjects for disease assessment and safety per the local practice. No efficacy data will be collected; only SAEs will be collected for safety on the SAE form as specified in Table 11. 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.

The assessments and timing are specified in the Time and Events Schedule (Table 11).

Table 11: Time and Events Schedule (Long-term Extension After Unblinding)

Procedures	Comments	Open-label Treatment Phase (until reaching criteria in Section 10.2, or termination of the study)	
		Continuing to Receive Niraparib +AAP (as single agents or combination tablet)	Receiving AAP alone
Informed Consent	All subjects must sign informed consent prior to entering the LTE Phase		
Study Drug Dispensing			
Open label Niraparib+AAP (or AAP)		Continuous; sufficient study drug until next visit will be dispensed[a]	
Study drug compliance		As per local standard of care	
Clinical Laboratory (Local Laboratory)			
Hematology and blood chemistry		Per local practice and local label for niraparib and AAP [b]	
Safety			
SAEs		Collection of SAEs; see Section 12 of protocol	

AAP=abiraterone acetate plus prednisone; AE=adverse events; EU=European Union; IWRS=interactive web response system; LTE=Long-Term Extension; SAE=serious adverse event; SmPC=Summary of Product Characteristics; USPI=United States Package Insert.

a. Dispensing of study drugs will occur every 1 to 6 months in accordance with local practice. Subjects will be supplied with 1 to 6 months of study drugs at each visit.
b. Whichever is more frequent

Attachment 7: Safety Data Collection Phase for Unblinded Cohort 2 Subjects Included in the Futility Analysis

With the implementation of Amendment 5, Cohort 2 subjects who have been unblinded will be switched over to a minimal collection schedule as described in Table 12.

After the sponsor's notification, Cohort 2 subjects still on study treatment will move from the Safety Data Collection Phase into the Long-Term Extension Phase of the study as described in Attachment 6.

Tumor assessments will be done as per local practice. Electronic PRO collection will cease.

Table 12: Time and Events Schedule (Data Collection for Unblinded Cohort 2 Subjects During the Treatment Phase)

Procedures	Comments	Treatment Phase (until reaching criteria in Section 10.2, termination of the study, or transfer into LTE Phase)	Follow-up Q3M up to 12 months after treatment discontinuation
Screening			
Informed consent	All subjects must sign the ICF for the Safety Data Collection Phase	X	
Study Drug Dispensing			
Open label Niraparib+AAP (or AAP alone)		Continuous; sufficient study drug until next visit will be dispensed	
Study drug compliance		X (via IWRS) Bottle(s) including any unused medication will be returned at every visit (every 3 cycles)	
Clinical Laboratory (Local Laboratory)			
Safety Labs[b]		Every 3 cycles	
Vital signs (HR and blood pressure)		At each visit	
Physical Examination		At each visit. Clinically relevant abnormalities should be reported as AEs.	
Adverse events/SAE		X[a]	
Survival		X	X
Efficacy			
Tumor assessments, PSA		Per local practice	

a. Continuous during this period and until 30 days after the last dose if discontinued during this period. Related SAE should continue to be reported in follow up.
b. Hematology Panel: hemoglobin, WBC count, platelet count, and ANC, Serum chemistry panel: potassium, creatinine, Liver function tests: AST, ALT, and total bilirubin

Note: The last visit of the Treatment Phase can be considered as the EOT visit

Attachment 8: Protocol Amendment History

Amendment 5 (29 January 2021)

The overall reasons for the amendment:
(a) To revise safety monitoring and guidance based on updates to the niraparib core safety information.
(b) To clarify the procedures for subjects moving into the Extension Phase (open label or long term)

Applicable Section(s)	Description of Change(s)
Rationale: To align with niraparib IB and product information.	
Time and Events Schedule 1: Procedures and Assessments	Addition of timepoints for vital signs (blood pressure [BP]) measurements; Footnote 'f' added for monitoring of blood pressure.
Rationale: To allow for data collection for food effects of the combination tablet.	
Time and Events Schedule 2: Pharmacokinetics Assessments	Added a footnote to specify that the time of most recent predose meal should be collected on C2D1 and C3D1 for Cohort 3.
Rationale: To align with the results of the futility analysis.	
Synopsis; 3.1.2 Cohort 2: Subjects with Metastatic Castration-resistant Prostate Cancer and No HRR Gene Alteration; 3.1.3 Cohort 3: Subjects With Metastatic Castration-resistant Prostate Cancer Receiving the Fixed-dose Combination of Niraparib and Abiraterone Acetate; 9.1.5 Futility Analysis for Cohort 2; 11 Statistical Methods	Amended the text to specify that futility was met for Cohort 2 and that no additional subjects would be enrolled in this cohort. Amended the text to specify preplanned analyses that will be performed based on the results of the futility analysis.
4.2 Inclusion Criteria (#1.2)	Inclusion criterion #1.2 was rephrased to clarify that only subjects positive for HRR gene alterations would be enrolled in Cohort 3.
Attachment 4	Updated the text to clarify that only subjects positive for HRR gene alterations would be enrolled in Cohort 3 and increased Cohort 3 sample size.
Rationale: To align with the definitions and methods of contraception described in the Clinical Trials Facilitation and Coordination Group (CTFG) guidelines.	
4.2 Inclusion Criteria (#9)	Amended text to clarify that study participants must agree to use an adequate contraceptive method or sexual abstinence, the details of which have been included under Section 4.4. Lifestyle Considerations. Clarified restrictions related to sperm donation.
Rationale: To align with niraparib safety information.	

4.3 Exclusion Criteria (#10)	Rephrased Exclusion criterion #10 to clarify that subjects with active or symptomatic viral hepatitis or chronic liver disease would be excluded from the study.
Rationale: To align with safety language in the niraparib IB.	
6.3.1 Non-hematologic Toxicities	Added instruction that the study drugs must be permanently discontinued if subject is reported with treatment-related hypertensive crisis.
6.3.1.3 Posterior Reversible Encephalopathy Syndrome (PRES)	Added new section regarding posterior reversible encephalopathy syndrome (PRES) and instructions for discontinuation of niraparib if PRES is diagnosed.
Rationale: To align with the prescribing information for the study drugs.	
6.4 Treatment of Overdose; References	Information regarding actions to be taken in case of study drug overdose was clarified.
Rationale: To align with protocol template.	
9.2.1 Sample Collection and Handling	Added instruction for analyses of genetic samples and confidentiality.
12 Adverse Event, Serious Adverse Event, and Other Safety Reporting; 13 Product Quality Complaint Handling; 16.2.3 Informed Consent; 17.8 Monitoring; 17.11 Use of Information and Publication	Updated sections per protocol template.
Attachment 8	Attachment for protocol amendment history added.
Rationale: To align with current study procedures.	
10.2 Discontinuation of Study Treatment	Added clarification that, after radiographic progression has been confirmed, subjects remaining on study treatment should undergo scans as per local standard of care.
10.3 Withdrawal from Study; Time and Events Schedule 1	Added clarification that sites may be contacted in between scheduled follow up to collect survival information.
Rationale: To align with dose modification guidelines.	
Attachment 4	Table 7, the minimum reduced AA dose was changed from ‘250 mg’ to ‘500 mg’.
Rationale: Information added regarding how to manage subjects after primary analysis.	
Attachment 5 and 6; Section 9.1.8	Open-label extension and long-term extension information added.
Rationale: To allow for limited data collection for subjects in Cohort 2 included in the futility analysis.	
Attachment 7	Updated data collection for Cohort 2 subjects.
Rationale: Minor changes, corrections, and errors were addressed throughout the protocol.	

Throughout the protocol	Minor revisions were made for improved clarity. Other minor errors and inconsistencies were revised, and grammatical, formatting, or spelling changes were made. Abbreviations and references were updated as needed. Consistent notation has been applied when referring to treatment regimen: niraparib and abiraterone acetate (AA) plus prednisone (AAP).

Amendment 4 (03 July 2020)

The overall reasons for the amendment:
(a) to update the statistical analysis of the study to allow evaluation of results for all subjects enrolled in the study combined. For the primary endpoint, subjects with breast cancer gene (BRCA)1 or 2 gene alterations (the BRCA subgroup) of Cohort 1 will be analyzed first. If statistical significance is reached in the BRCA subgroup, then the entire population of subjects with homologous recombination repair (HRR) gene alterations (Cohort 1) will be tested. If statistical significance in Cohort 1 is reached and futility has not been met in Cohort 2, then the combined population of Cohort 1 and Cohort 2 (Intent-to-Treat [ITT] population) will be tested.
(b) to enroll a new cohort of subjects (Cohort 3) who will receive a fixed-dose combination (FDC) tablet formulation of niraparib and abiraterone acetate (AA) with the objective of describing the efficacy and safety of the FDC tablets within this ongoing study.

Note: where mentioned in the Amendment 4 summary below, Cohort 1= Subjects with Metastatic Castration-resistant Prostate Cancer (mCRPC) and HRR Gene Alteration; Cohort 2= Subjects with mCRPC and No HRR Gene Alteration; and Cohort 3= Subjects with mCRPC (with or without HRR Gene Alteration) Receiving the FDC of Niraparib and AA. For the sake of brevity, these cohort descriptions will not be repeated each time.

Applicable Section(s)	Description of Change(s)
Rationale: To add a new cohort of subjects (Cohort 3) who will receive the FDC tablet formulation of niraparib and AA and to describe the efficacy and safety of the FDC tablets within this ongoing study. This cohort will not be part of the ITT or Safety population and will be described separately.	
Synopsis (Overview of Study Design); 3.1. Overview of Study Design; 3.1.3. Cohort 3; 4.2. Inclusion Criteria; 11.1. Analysis Populations; 14. Study Drug Information; Attachment 4: Open-label Fixed-dose Combination- Cohort 3	Description of Cohort 3 and related study procedures for this cohort have been added.
Rationale: The study was originally designed to test Cohorts 1 and 2 separately. To allow evaluation of results for all subjects enrolled in the study combined, the statistical plan is being updated.	

Applicable Section(s)	Description of Change(s)
Synopsis (Hypothesis, Overview of Study Design, Study Populations, Statistical Methods); 2.1. Objectives and Endpoints/Assessments; 2.2. Hypothesis; 3.1.1. Cohort 1; 3.1.2. Cohort 2; 9.1.4.1. Futility Analysis for Cohort 2; 11. Statistical Methods; 11.1. Analysis Populations; 11.2. Sample Size Determination; 11.2.3. Secondary Endpoints at Primary rPFS Analysis; 11.3. Efficacy Analyses; 11.3.1. Cohort 1; 11.3.2. Cohort 2; 11.10. Interim Analysis	Hypothesis was revised. Statistical analysis assumptions and power calculations were revised. Study population definition was revised for the ITT Population and defined for the FDC Population. Additional detail has been provided for the planned efficacy analyses, with reference to the Statistical Analysis Plan. Revisions to the planned interim analysis were made. Table 1 revised to indicate objectives and endpoints apply to subjects in Cohort 1 and the ITT Population. Clarified that subjects with ATM alterations who have already been enrolled will remain in Cohort 1. Clarified that the futility analysis is non-binding for Cohort 2. Deleted Section 11.2.3. Secondary Endpoints at Primary rPFS Analysis. Combined Sections 11.3.1. (Cohort 1) and 11.3.2. (Cohort 2) into new Section 11.3.1. Endpoints. Removed redundant text. Defined that the ITT population and Safety population include subjects in Cohorts 1 and 2; the safety and efficacy of Cohort 3 will be described separately. Section 11.2.3. Secondary Endpoints at Primary radiographic progression-free survival Analysis and Sections 11.3.1. Cohort 1 and 11.3.2. Cohort 2 have been removed. Table 8 (Power to Declare Significance) and Table 9 (Probability that the Observed HR<1 for Secondary Endpoints) have been removed.

Rationale: The wording “DRD” will be updated to HRR gene alteration given that patients whose tumors have mutations in genes outside the DNA repair pathway (eg, cyclin-dependent kinase 12 [CDK12]) may be included for enrollment in Cohort 1 of the study. Inclusion of CDK12 and broadening of the biomarker selected population is based upon data from the PROfound study, and United States Food and Drug Association approval of olaparib in a broad panel of genes including CDK12.

Throughout the protocol	DRD replaced with HRR gene alteration.

Rationale: To allow consideration of previously obtained results from sponsor’s required assay for determination of biomarker eligibility. To ensure a homogenous ITT population, blood and tumor tissue will still be collected and analyzed by the sponsor’s assays.

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of Study Design); 3.1. Overview of Study Design; 3.2.3. Biomarker Collection; 4.2. Inclusion Criteria; 5.1. Treatment Allocation; 9.1.2. Prescreening Phase for Biomarker Evaluation; 9.5. Biomarkers; Table 5	Text added that indicates subjects may provide a previous result from the sponsor's required assays for biomarker screening. Germline test has been replaced with local result/test. Added text indicating that blood and tumor tissue should be collected and submitted for all subjects.
Rationale: To align visit cycles with imaging visits and to allow more flexibility for patient-reported outcome (PRO) assessments during the Follow-up period.	
Time and Events Schedule 1: Procedures and Assessments	Changed Cycle numbers.
Time and Events Schedule 3: PROs	Changed cycle numbers and added visit windows for PRO assessments during the Follow-up period. In footnote 'a', removed the text indicating that BPI-SF#3 should also be completed at any unscheduled visits.
Rationale: To provide an update of the sponsor's clinical studies for niraparib.	
1.1. Background and Design Rationale; 1.2. Summary of Available Clinical Data for Niraparib; 1.4. Summary of Available Clinical Data for Niraparib in Combination With Abiraterone Acetate and Prednisone/Prednisolone; 3.2.1. Selection of Dose	Provided updates for Study 64091742PCR1001 (BEDIVERE), Study 64091742PCR2002 (QUEST), and Study (67652000PCR1001, a new bioavailability and bioequivalence study that will support the development of the FDC tablet formulation).
Rationale: To include an additional biomarker to the panel of study biomarkers.	
9.5. Biomarkers	Added CDK12 to Table 4: Biomarker Panel and Criteria for Positivity.
Rationale: To allow more flexibility for subjects to provide informed consent.	
16.2.3. Informed Consent	Text has been revised to clarify that subject consent can include remote/virtual consent or written consent.
Rationale: Minor errors, editorial issues, or changes for clarity/consistency noted in the protocol were corrected. To maintain consistency with Company protocol template.	

Applicable Section(s)	Description of Change(s)
Abbreviations;	Updated to be consistent with protocol text.
9.8. Safety	Updated footnote in list of laboratory assessments.
12.3.1. All Adverse Events	Deleted text related to disease progression as this is described in Section 12.3.4. Disease Progression and Death.
12.3.4. Disease Progression and Death;	Updated text consistent with protocol template language.
14.1. Physical Description of Study Drug(s)	Added text that placebo and AA tablets will be manufactured and provided by the sponsor.
14.2. Packaging	Added packaging information for AA 250 mg tablets.
Throughout protocol	Double-blind Treatment Phase changed to Treatment Phase to account for Cohort 3.

COVID-19 Appendix (v2.0) (11 June 2020)

The overall reason for the appendix: to provide guidance on virtual consenting and clarify guidance with respect to direct-to-patient (DTP) shipment of drug supplies 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 11 June 2020, was applied to implement this COVID-19 Appendix.	
COVID-19 Appendix (v2.0)	Modified text related to informed consent procedures and DTP shipment of drug supplies.

COVID-19 Appendix (v1.0) (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 (v 1.0)	The standalone Appendix provides guidance to investigators for managing study-related procedures during the SARS-CoV-2 pandemic.

Amendment 3 (12 February 2020)

The overall reason for the amendment: To stop enrollment of subjects with ATM mutations into Cohort 1 and to ensure at least 50% of Cohort 1 are subjects with BRCA mutations.

Applicable Section(s)	Description of Change(s)
Rationale: External data suggest that subjects with ATM mutations may not derive benefit from treatment with PARP inhibitors alone. Therefore, further enrollment of subjects with ATM mutations will be stopped. In addition, the PARP inhibitors have demonstrated the most benefit in subjects with BRCA mutations, and therefore, subjects with BRCA1 or BRCA2 mutations will be the chosen subgroup for the Song and Chi analysis (and will represent at least 50% of Cohort 1 enrollment).	
Synopsis Overview of Study Design; Statistical Methods; 11.2.1. and 11.3.1. Cohort 1: Subjects with Metastatic Castration-resistant Prostate Cancer	Added text indicating that the chosen subgroup for the Song and Chi analysis will be subjects with BRCA1 and BRCA2 mutations.
9.5. Biomarkers	Added text indicating the enrollment of subjects with ATM mutations will be stopped.
Rationale: To decrease the frequency of study assessments to ease subject burden.	
Time and Events Schedule 1: Procedures and Assessments	Modified to reduce the frequency of assessments after Cycle 25 to every 3 Cycles. Footnote added to clarify timing of CBC and LFT evaluations.
Rationale: To allow positive BRCA1 or BRCA2 germline testing results from certified laboratories as acceptable for screening. This will allow subjects with known pathogenic BRCA mutations to begin screening procedures.	
3.2.3. Biomarker Collection; 9.5. Biomarkers	Added text that subjects with germline positive pathogenic BRCA1 or BRCA2 results from certified laboratories may enter screening.
4.2. Inclusion Criteria	Modified Inclusion Criteria 1.1 to allow germline testing for BRCA
Rationale: To more clearly describe protocol procedures and update text consistent with Janssen procedures for safety reporting and review.	
Throughout the protocol	Text has been revised or reorganized for clarity, as needed.
10.2. Discontinuation of Study Treatment	Text has been revised to more clearly describe study treatment discontinuation conditions and procedures.
Attachment 3	Updated instructions for reporting of anticipated events and review of same by the Safety Assessment Committee.

Amendment 2 (30 September 2019)

The overall reason for the amendment: To change the secondary endpoints of the study to include quality-of-life impacting events and procedures that objectively evaluate the treatment effect of niraparib.

Applicable Section(s)	Description of Change(s)
Rationale: Clinical practice patterns with regards to pain management have changed such that initiation and duration of opiate use is no longer a meaningful clinical proxy for worsening cancer pain. Options such as available alternative anti-cancer treatments, palliative external beam radiation or radionuclide therapy and bone strengthening agents (eg, denosumab) are now increasingly used to better target cancer pain, rather than mask pain with the use of opioids. Similarly, pain progression, as defined by an increase in patient-reported pain or initiation of opiate use, may overlook many clinically meaningful events given that patients may have their cancer-related pain effectively managed through non-opiate interventions. Time-to-symptomatic progression, which includes events that can significantly affect a patient's quality of life (eg, prostate cancer progression leading to fractures and local symptoms such as bladder outlet obstruction requiring medical intervention), is a more clinically relevant assessment of the patient's disease experience. This endpoint can better reflect an improvement in patient symptoms when they are treated with the combination of niraparib and abiraterone acetate plus prednisone (AAP) versus AAP alone. In order to better evaluate disease-related symptoms that affect a patient's life, the secondary endpoints of time-to-chronic opioid use and time-to-pain progression have been removed and replaced with time-to-symptomatic progression, an endpoint that can provide a more comprehensive, objective, and patient-relevant measure of worsening disease.	
Synopsis Primary Objectives, Endpoint, and Hypotheses; 2.1. Objectives and Endpoints/Assessments; 11.3.3. Endpoints; Attachment 3: Anticipated Events	Previous "other" endpoint "Time-to-symptomatic progression" has been moved to a secondary endpoint to assess clinical benefit of niraparib and AAP compared to placebo and AAP. The time-to-symptomatic progression endpoint definition was also modified. The definition of fracture was clarified as symptomatic and/or pathological, and pathological fracture was removed from the list of anticipated events. Removed secondary objectives, endpoints/assessments from the Synopsis. "Time-to-chronic opioid use" has been deleted as a secondary endpoint.
Synopsis Evaluations; 9.1.6. Follow-up Phase; 9.2.1.2. Evaluations for Other Efficacy and Patient-reported Outcome Endpoints; 11.3.3. Endpoints	Added "symptomatic progression" to list of efficacy evaluations. Deleted text regarding collection of analgesic use.
Rationale: To remove the requirement for subjects to have a prolonged visit without compromising the scientific rigor of the pharmacokinetic (PK) analysis.	
Time and Events Schedule 2: Pharmacokinetic Assessments	Removed Cycle 2 PK collection timepoint of +3-6 hours.
Rationale: To simplify the timing for collection of BPI-SF information to a monthly/per cycle basis.	

Applicable Section(s)	Description of Change(s)
Time and Events Schedule 3: Patient-reported Outcomes; 9.6. Patient-reported Outcomes 15. Study-specific Materials	Added Screening as a timepoint of BPI-SF collection and revised footnote 'a' of T&E Schedule 3 to further clarify the timing for BPI-SF collection. Hand-held device for PRO collection has been removed.
Rationale: Minor changes, corrections, and errors were noted.	
Time and Events Schedule 1: Procedures and Assessments	A few timepoints for the collection of treatment compliance and serum PSA were removed.
1.2. Summary of Available Nonclinical and Clinical Data for Niraparib	Updated the potential risks of niraparib based on current known information in the Investigator's Brochure.
4. Subject Population	Clarified text to include local legal age of consent.
4.2. Inclusion Criteria	Criterion 3: "Progression of metastatic prostate cancer" was changed to "Metastatic prostate cancer." Text "at study entry" was removed in the context of metastatic prostate cancer in the setting of castrate levels of testosterone or bilateral orchiectomy. Criterion 7.1.e: Unit of 1.73 m^2 was removed as it was included in error. Criterion 7.1.h: AST/ALT inclusion criteria corrected to ≤3x upper limit of normal (ULN).
4.3. Exclusion Criteria; 9.1.3. Screening Phase	Criterion 2.1: Provided further clarification of excluded systemic therapies in the mCRPC setting. Criterion 31: Clarified the exclusion for subjects with evidence of PSA progression who received 2 to 4 months of AAP prior to randomization for the treatment of mCRPC.
5.1. Treatment Allocation	Examples of past AR-targeted exposure revised to novel anti-androgen therapy.
6.1. Study Drug Administration	Removed restriction for consuming liquids and clarified how to handle missed doses.
6.2. Special Dosing Instructions for Pharmacokinetics Visits; 9.3.1. Sample Collection and Handling	Clarified study drug dosing instructions on PK collection days.
6.3.1 Non-hematologic Toxicities, Table 2	Added guidance for abiraterone acetate dosing in the event of a Grade 4 ALT increase. Updated footnote.
7. Intervention Compliance	Guidance regarding dosing non-compliance was updated to reflect the current practice in the Janssen Phase 3 prostate cancer program.
8.1. Prohibited Concomitant Medications	Radiotherapy prohibition clarified to "Radiotherapy for tumor progression. May receive radiotherapy in selected cases after discussion with sponsor."

Applicable Section(s)	Description of Change(s)
9.1.2. Prescreening Phase for Biomarker Evaluation	Clarified that additional plasma or tissue samples may be requested if the sample obtained to determine eligibility fails to produce a conclusive result.
9.1.3. Screening Phase	Removed requirement for obtaining a new ICF before rescreening. Added text indicating that initial screening results could be used to determine eligibility if obtained within 6 weeks of planned enrollment.
9.1.6. Follow-up Phase	Text revised that CT/MRI and bone scans should be collected every 3 months until confirmed radiographic progression or initiation of subsequent therapy (text "will" deleted).
9.2.1.1. Evaluations for Primary Endpoint	Text clarified to indicate that rPFS will be assessed by blinded independent central review using CT or MRI and whole-body scans. Investigator-assessed rPFS will be based on data collected on imaging assessment electronic case report forms (eCRFs).
9.5. Biomarkers; Table 4	Text for genomic lesions required for positivity revised to include loss of heterozygosity. Table 4 and footnotes updated.
9.5.1. Evaluations; 9.5.1.2. Plasma for DNA; 9.5.1.3. Tissue Analysis	Clarified that any remaining exploratory biomarker samples (including CTC, DNA, and RNA) collected may be used for future studies. Clarified that plasma DNA from biomarker eligibility panel or tumor tissue may be used to further develop the diagnostic test to identify patients suitable for treatment with therapeutic regimens that contain niraparib.
9.8. Safety, Clinical Laboratory Tests	Updated requirements for the hematology report in cases of MDS/AML. New text added to footnote "a" outlining testing requirements for positive hepatitis B/hepatitis C screening results.
9.8. Safety, Electrocardiogram (ECG)	Clarified that ECGs should be obtained when serum potassium levels are within normal limits.
10.3. Withdrawal from the Study	Text added to indicate that subject survival status may be obtained by public record or cancer registry where permitted by local regulations.
11.7. Patient-reported Outcomes Analyses; Table 9	Table 9 was revised to clarify the direction of the score (higher scores meaning deterioration), and thresholds were added for EQ5D and EQVAS.
12.3.1. All Adverse Events; Time and Events Schedule 1: Procedures and Assessments	Removed the requirement to report death from any cause during the Prescreening Phase.
14.2. Packaging	Text updated to indicate that prednisone will be packaged in blister packs or bottles with child-resistant closures.
14.4. Preparation, Handling, and Storage	Text outlining handling and impact of niraparib on the composition of semen and fetus in utero revised for readability.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Applicable Section(s)	Description of Change(s)
Attachment 3: Anticipated Events	Removed pathological fracture, spinal cord compression, cauda equine syndrome, ureteric obstruction, and urethral obstruction from the list of anticipated events since these will now be reported as part of the time-to-symptomatic progression endpoint.

Amendment 1 (10 April 2019)

The overall reason for the amendment: The overall reason for the amendment is to 1) clarify collection of Brief Pain Inventory-Short Form #3 (BPI-SF #3) assessments during the screening period, 2) add Patient-reported Outcome(s) Common Terminology Criteria for Adverse Events (PRO-CTCAE) assessments for subjects in the US, 3) remove text regarding MDS/AML evaluation to clarify that the tests are done locally and not centrally, and 4) implement administrative changes based on local regulations

Applicable Section(s)	Description of Change(s)
Rationale: To clarify timing of imaging assessments.	
Synopsis (Overview of study design); Time and Events Schedule 1; 3.1 Overview of Study design	Updated text to state that imaging will be performed every 8 weeks for the first 24 weeks.
Rationale: To allow for appropriate exploratory biomarker analyses according to local regulations.	
Synopsis (Evaluations); Time and Events Schedule 1; 3.2.3 Biomarker Collection; 9.5.1 Evaluations	Added text to state appropriate biomarker analyses could be performed “where allowed by local regulations”.
Rationale: To clarify collection of BPI-SF#3 assessments from Screening to C1D1.	
Time and Events Schedule 3; 9.6 Patient-reported Outcomes	Updated text regarding the timing of BPI-SF#3 assessments.
Rationale: To add exploratory PRO-CTCAE assessments for subjects in the US	
Time and Events Schedule 3; 2.1 Objectives, Endpoints, and Hypotheses; 9.6 Patient-reported Outcomes; 11.7 Patient-reported Outcomes Analyses	An objective was added to evaluate the subjects’ experience regarding treatment-related symptoms and tolerability. Information regarding the collection of PRO-CTCAE assessments was added in the Time and Events Schedule 3 and in other parts of the protocol, as applicable.
Rationale: To accommodate local differences in age of consent.	
4.1 Prescreening eligibility criteria	Added text to include “or the local legal age of consent”.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that the tests for MDS/AML are done locally and not centrally.	
9.8 Safety	Deleted text requiring central collection of whole blood samples for cytogenetic analysis.
Rationale: To accommodate local methods of reporting.	
12.3.2 Serious Adverse Events	Added that reports of a serious adverse event could be reported through fax.
Rationale: Enrollment assignments for each cohort based on biomarker status were clarified.	
9.5 Biomarkers	Updated text in Table 5.
Rationale: To clarify that additional laboratory testing will be allowed if clinically indicated.	
9.8 Safety	Added text to allow for additional testing after discussion with the medical monitor.
Rationale: To ensure consistency between the Time and Events Schedule 1 and the protocol body text, weight assessment was removed.	
9.8 Safety	Removed weight assessment from physical examination assessments.
Rationale: Minor changes, corrections, and errors were addressed throughout the protocol.	
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 drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: 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 course of 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	30-Sep-2021 20:37:30 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Subjects with Metastatic Prostate Cancer

MAGNITUDE

Protocol 64091742PCR3001; Phase 3

JNJ-64091742 (niraparib)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

Status: Approved
Date: 11 June 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-34072, 2.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL 64091742PCR3001 (EDMS-ERI-146329771)

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered to be at risk, study intervention may be interrupted or discontinued.

Scheduled visits that cannot be conducted in person at the study site may be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects should be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects may also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the subject and investigator, and with the agreement of the sponsor. Examples of modifications are presented under the **GUIDANCE SPECIFIC TO THIS PROTOCOL**. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

These provisions are meant to minimize the risk of exposure to COVID-19 and to safely maintain subjects on study treatment while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

1. STUDY VISITS - GENERAL

- To protect study subjects from being unnecessarily exposed to COVID-19 at sites that have been affected, those subjects who are doing well and for whom there is no safety concern may have tele-health visits (conducted via phone or computer). Normal study procedures (eg, Eastern Cooperative Oncology Group assessment, adverse event reporting) should be followed for the applicable visit as possible. Regular blood pressure monitoring can be performed at home, if possible. Other programs may be implemented by or with approval from the sponsor, such as Home Health Care Visits for study assessments and procedures (eg, physical exam, lab draws, etc), where feasible and permissible by local policy and regulations.
- The benefit of continuing treatment should be balanced with the risks of treatment without the usual clinical supervision. For subjects who have recently had adverse events that required a study drug interruption or dose reduction, or for those subjects who are at increased risk for severe COVID-19 infection based on age or comorbidities, a temporary interruption of study drugs (particularly niraparib/placebo) should be considered by the investigator and documented in the source and electronic CRF (eCRF).
- Consenting and re-consenting of subjects will be performed as applicable (including remote consenting by phone or video consultation) and according to local guidance for informed consent as applicable.

2. PRESCREENING, SCREENING, AND RANDOMIZATION

- Prescreening, screening, and randomization to the study may continue during the COVID-19 pandemic if the benefits of study treatment outweigh the risks, as per the investigator's assessment. If it is anticipated that the situation may worsen at the site and that health care capacities may become more limited, then screening and randomization should be delayed for subject safety. When randomization occurs at the site, the screening procedures may be utilized after discussion with the sponsor, despite being out of window.

3. STUDY VISITS – ASSESSMENTS

- If possible, central safety laboratory testing is to be continued. However, if central laboratory tests cannot be performed, the use of a local laboratory is allowed for study evaluations. A copy of the local laboratory report should be reviewed by the investigator and retained, along with the reference ranges, for the source documentation and documented in the eCRF. If research-specific blood collection is not possible (eg, biomarker, pharmacokinetics collection), then the missed sample should be documented as a deviation.
- If visits are conducted remotely, then electronic patient-reported outcomes (ePRO) information should be collected via phone using interview mode on the site tablet.

- If safe to do so, then subjects should come to their usual site for imaging visits. If imaging cannot be performed at the site due to travel restrictions, the use of a local facility close to the subject's home is permitted, but provision of scans to the investigative site should be arranged and documented. If no imaging is possible, the missed visit should be documented as a deviation, and imaging should be resumed when possible.

4. STUDY DRUG SUPPLY

- For subjects able to visit the clinic/hospital, but who request to reduce visit frequency, an additional supply of study drugs can be provided.
- For subjects unable to visit the clinic/hospital, direct-to-patient (DTP) shipment of study drugs may be implemented, where allowed per local regulations and if requested by the treating study physician. Where DTP shipments are deemed necessary, the process should be coordinated between the site and sponsor staff following standard DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.

5. EXPOSURE TO COVID-19

- If a subject develops COVID-19 infection, niraparib/placebo should be interrupted until the infection resolves. Abiraterone acetate plus prednisone can be continued at the investigator's discretion.
- Resumption of treatment: When a subject recovers from suspected or confirmed COVID-19 infection, niraparib/placebo may be resumed when safe to do so as determined by the study physician in consultation with the sponsor prior to resuming niraparib/placebo.
- COVID-19 infection should be reported to the sponsor and follow the usual Adverse Event/Serious Adverse Event reporting requirements.

6. REPORTING OF PROTOCOL DEVIATIONS

All deviations from the study protocol will be reported based on standard guidance. If related to the COVID-19 pandemic situation, these deviations will be recorded as COVID-19 related by the sponsor.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-64091742 (niraparib) Clinical Protocol 64091742PCR3001

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

Institution: Janssen Research & Development

Signature: PPD PPD Date: _____
(Day Month Year)

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 5
Status: Approved, Date: 11 June 2020