Janssen Research & Development

Statistical Analysis Plan

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

Protocol 64091742PCR2002; Phase 1b-2

JNJ-64091742 (niraparib)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

Draft: March 16, 2021

ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	total systemic clearance
C_{max}	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IQ	interquartile
IVRS	interactive voice response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRD	minimum required dilution
NAb	neutralizing antibodies
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
RP2D	Recommended Phase II Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
US NCI	United States National Cancer Institute
V	volume distribution
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization

1. INTRODUCTION

This document describes the planned statistical analyses for protocol 64091742PCR2002: A Phase 1b-2 Study of Niraparib Combination Therapies for the Treatment of Metastatic Castration-Resistant Prostate Cancer.

This study will evaluate safety and efficacy of niraparib in combination with other anti-cancer agents. Combination 1 combined niraparib with anti-PD-1 monoclonal antibody, cetrelimab (JNJ-63723283). Combination 2 combined niraparib with ZYTIGA® (abiraterone acetate) plus prednisone (referred to as AAP). Combination 1 and 2 were closed to enrollment. Combination 3 will combine niraparib plus abiraterone acetate in 3 fixed-dose combination (FDC) tablets (CJNJ-67652000). The sponsor may amend this study in future to investigate additional niraparib combination therapies, if and when scientific data are available to support such studies.

This statistical analysis plan (SAP) is intended to supplement the study protocol. Any deviations from this analysis plan will be described in the clinical study report.

1.1. Trial Objectives

For Combination 1, the study consists of two parts: Part 1 will support the dose selection for the niraparib and cetrelimab combination therapy; Part 2 (dose expansion) will evaluate the recommended Phase 2 dose (RP2D) of niraparib and cetrelimab when given in combination in an expanded number of subjects. The overall objectives and endpoints for the two parts in the study are provided in Table 1 and Table 2.

Table 1: Primary Objectives and Endpoints for Part 1, Niraparib and Cetrelimab

Objectives	Endpoints
Primary	
• To evaluate the tolerability of niraparib combination therapies for the treatment of mCRPC • Determine the RP2D of niraparib combination therapies	• Incidence of specified toxicities
Secondary	
• To characterize the PK and immunogenicity (if applicable) of niraparib combination therapies	• Plasma concentrations of niraparib and, if performed, its major metabolite (M1), and plasma or serum concentrations of the combination agent • Population PK parameters and derived exposure of niraparib and combination agent • Anti-drug antibodies (if applicable)
Abbreviations: mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetics; RP2D=recommended Phase 2 dose	

Table 2: Primary Objectives and Endpoints for Part 2, Niraparib and Cetrelimab

Objectives	Endpoints
Primary	
• To evaluate the antitumor effect of the RP2D of niraparib combination therapies for the treatment of mCRPC	• Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by RECIST 1.12 with no evidence of bone progression according to PCWG3 criteria[3]
• To evaluate the safety of the RP2D of niraparib combination therapies for the treatment of mCRPC	• Incidence and severity of AEs
Secondary	
• To evaluate other response outcomes of niraparib combination therapies for the treatment of mCRPC	• Composite response rate : defined as 1 of the following by PCWG3: – Objective response (confirmed per RECIST 1.1[2]), or – CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later, or – PSA decline of ≥50%, measured twice 3 to 4 weeks apart • CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later
• To evaluate duration of response	• Duration of objective response: time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first • rPFS: time from enrollment to radiographic progression or death from any cause, whichever occurs first
• To characterize the PK and immunogenicity (if applicable) of niraparib combination therapies through sparse sampling	• Plasma concentrations of niraparib and, if performed, its major metabolite (M1) when dosed with combination agent • Population PK parameters and derived exposure of niraparib and combination agent • Anti-drug antibodies (if applicable)
Exploratory	

• To evaluate MOAs for niraparib combination therapies, as well as potential biomarkers predictive of response and resistance	• Assessment of biomarkers related to MOAs or response/resistance for niraparib, other anticancer agent, or the combination at baseline, on treatment, and at progression
• To explore potential relationships between the PK of niraparib combination therapies, and any associated clinical activity, pharmacodynamic markers, or safety signals	• Changes in levels of pharmacodynamic markers (e.g., PSA, CTCs)
Abbreviations: AE=adverse event; CR=complete response; CTC=circulating tumor cell; mCRPC=metastatic castration-resistant prostate cancer; MOA=mechanism of action; ORR=objective response rate; rPFS=radiographic progression-free survival; PCWG3=Prostate Cancer Working Group 3; PR=partial response; PK=pharmacokinetics; PSA=prostate-specific antigen; RECIST= Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; RR=response rate	

The overall objectives and endpoints/assessments for Combination 2 is provided in Table 4.

Table 3: Objectives and Endpoints for Niraparib and Abiraterone/Prednisone

Objectives	Endpoints
Primary	
• To evaluate the antitumor effect of the RP2D of niraparib combination therapies for the treatment of mCRPC	• Composite Response Rate : defined as 1 of the following by PCWG3: – Objective response (confirmed per RECIST 1.1[2]), or – CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ⩾1 at baseline or CTC<5 per 7.5 mL with CTC ⩾ 5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later, or – PSA decline of ⩾50%, measured twice 3 to 4 weeks apart
• To evaluate the safety of the RP2D of niraparib combination therapies for the treatment of mCRPC	• Incidence and severity of AEs

Secondary	
• To evaluate other response outcomes of niraparib combination therapies for the treatment of mCRPC	• Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by RECIST 1.12 with no evidence of bone progression according to PCWG3 criteria[3] • CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ≥1 at baseline or CTC<5 per 7.5 mL with CTC ≥5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later
• To evaluate duration of response	• Duration of objective response: time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first • rPFS: time from enrollment to radiographic progression or death from any cause, whichever occurs first
Abbreviations: AE=adverse event; CR=complete response; CTC=circulating tumor cell; mCRPC=metastatic castration-resistant prostate cancer; MOA=mechanism of action; ORR=objective response rate; rPFS=radiographic progression-free survival; PCWG3=Prostate Cancer Working Group 3; PR=partial response; PK=pharmacokinetics; PSA=prostate-specific antigen; RECIST= Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; RR=response rate	

The overall objectives and endpoints/assessments for Combination 3 is provided in Table 5.

Table 4: Objectives and Endpoints for Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

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

1.2. Trial Design

This is a Phase 1b-2, multicenter, open-label study to select the RP2D of niraparib in combination with JNJ63723293 (cetrelimab), followed by dose expansion that will enroll adult subjects with mCRPC who are either biomarker positive (BM+) or biomarker negative (BM-) for DRD or BM+ for CDK12 pathogenic alterations. JNJ63723293 Study treatment will be administered on a 28-day cycle.

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

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

1.2.1. Combination 1: Niraparib and Cetrelimab

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

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

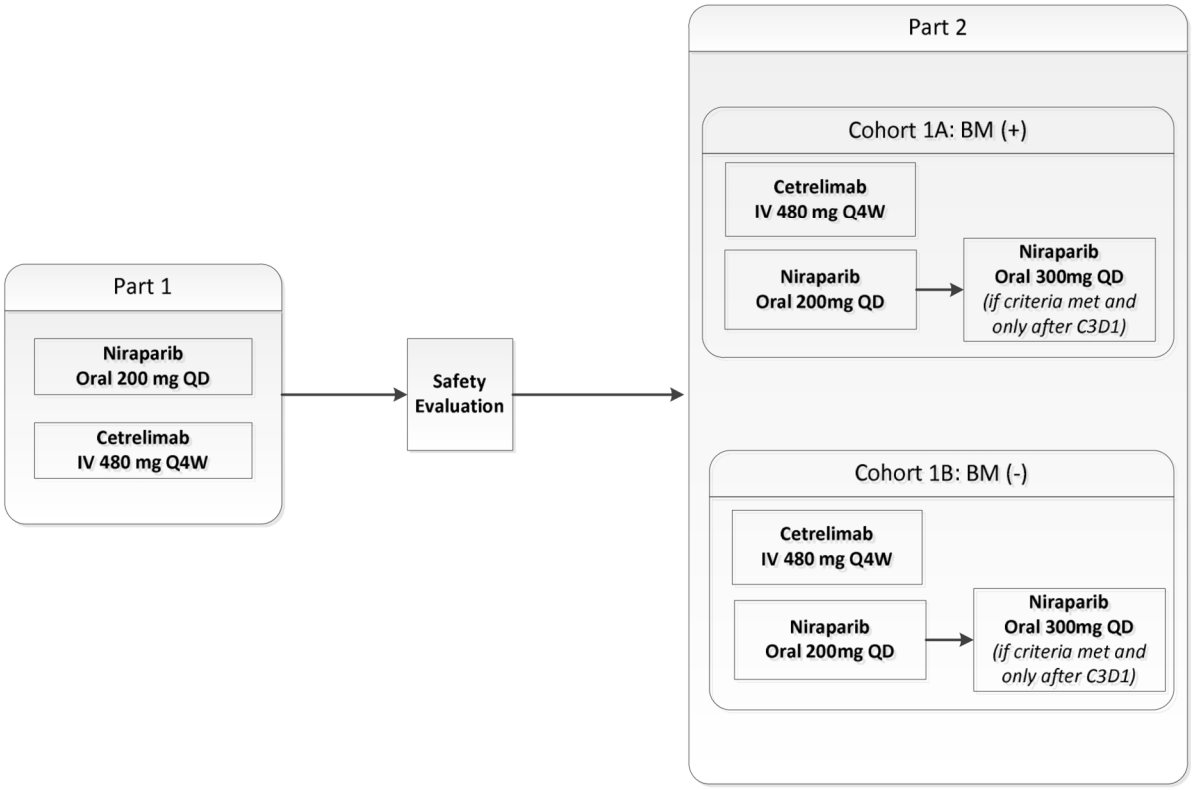
Evaluable subjects for Part 1 are defined as those who have an event as defined by the safety evaluation criteria in Cycle 1, or complete at least 1 cycle of treatment and receive at least 75% of the planned study drugs (ie, 75% niraparib capsules and 75% of cetrelimab infusion/s). Non-evaluable subjects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

should be transitioned to cetrelimab 480 mg every 4 weeks once the protocol amendment and revised informed consent form (ICF) are approved at the site, as required by local regulations.

Once an RP2D has been established for the combination in Part 1, approximately 30 subjects will be enrolled per cohort for Part 2. Note that a futility analysis was performed for Cohort 1B after approximately 10 subjects have been enrolled and evaluated in Part 2, the analysis result showed that a response rate of 13% was not achieved. All subjects will be assigned to a cohort based on their biomarker status for DRD or CDK12 (i.e., Cohort 1A=BM+ or Cohort 1B=BM-), which will be determined during the Prescreening Phase using the sponsor blood or tissue assay.

If a dose of niraparib 200 mg once daily is selected for the RP2D, then all subjects may receive an escalated dose of niraparib 300 mg once daily on or after Cycle 3 Day 1, if they meet the following criteria: platelets ≥100 x 109/L, hemoglobin ≥9.0 g/dL, and neutrophils ≥1.5 x 109/L for all laboratory tests performed during the first 2 cycles after discussion with the medical monitor.

Figure 1: Schematic for Combination 1



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

Based on the results of a pre-planned futility analysis, Cohort 1B was closed to enrollment on 30 May 2019. Based on Data Review Committee (DRC) review and recommendation from a meeting on 8 July 2020, Cohort 1A was also closed to enrollment. The subject is considered to have

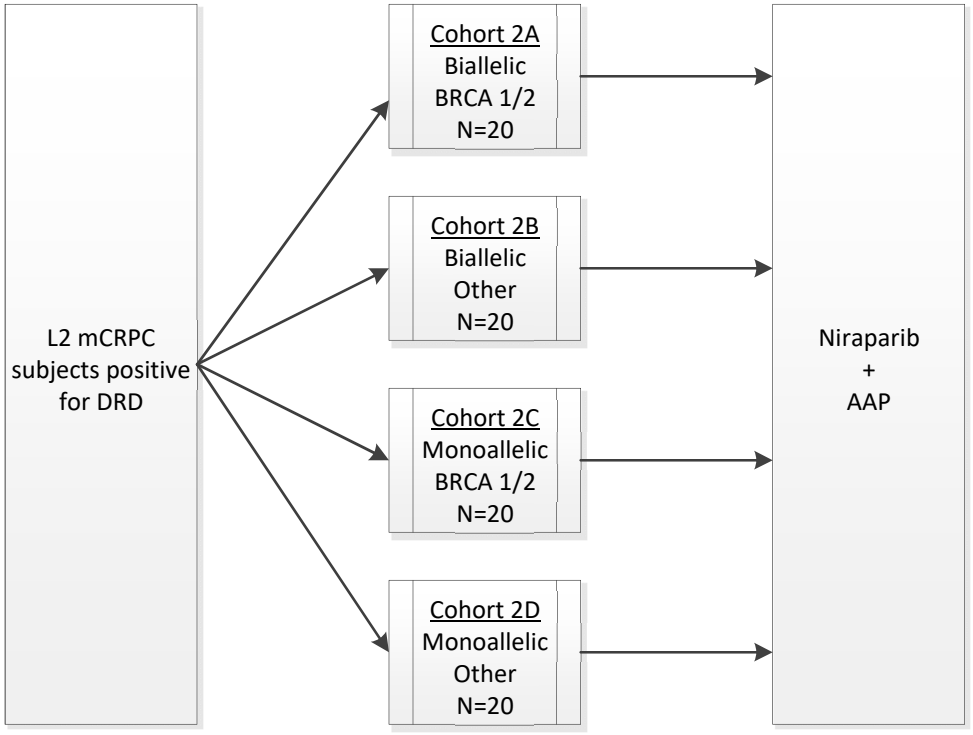
completed the study after discontinuing treatment for any reason and having had a safety assessment at the End-of-treatment Visit or the subject is lost to follow-up.

1.2.2. Combination 2: Niraparib and AAP

The RP2D for niraparib plus AAP was established in Study 64091742PCR1001. Therefore, Part 1 was not conducted in this study for Combination 2.

Combination 2 will explore the safety and efficacy of niraparib plus AAP in mCRPC patients with DRD as determined during the Prescreening Phase using a blood or tissue assay. In Part 2, subjects will be enrolled into 4 cohorts (BRCA biallelic loss [2A], other DRD biallelic loss [2B], BRCA monoallelic loss [2C], and other DRD monoallelic loss [2D]), with approximately 20 subjects in each cohort. A schematic for this combination is provided in Figure 2.

Figure 2: Schematic for Combination 2



Combination 2 has been closed to enrollment. The subject is considered to have completed the study after discontinuing treatment for any reason and having had a safety assessment at the End-of-treatment Visit or the subject is lost to follow-up.

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

Combination 3 is an open-label, multi-center, partly randomized (Cohort 1 only), parallel group study to determine the PK and safety of 3 FDC tablet formulations of niraparib+AA in men with mCRPC. The study will consist of a 21-day Screening Phase to determine eligibility, an open-label

PK Assessment Phase of 8 days (Study Days 1-8, inclusive), followed by an Extension Phase during which treatment will be continued from Cycle 1 Day 1 (Study Day 8) until discontinuation. Treatment will be continued from Cycle 1 Day 1 (Study Day 8) until discontinuation.

During the PK Assessment Phase, 3 cohorts will be studied. The Study Design is presented in Table 4 below.

- Cohort 1: subjects (N=34) will be randomized to receive a single dose of niraparib plus AA (200 mg niraparib + 1,000 mg AA) given as FDC1 regular-strength tablet formulation (G010) (Treatment Arm B [Cohort 1B], N=17) or as SAs (Treatment Arm A [Cohort 1A], N=17). Relative BA of the FDC1 regular-strength tablet will be assessed by comparing PK results from Cohort 1A to Cohort 1B.

- Cohort 2: subjects (N=17) will be assigned to receive a single dose of niraparib plus AA (200 mg niraparib + 1,000 mg AA) as FDC2 regular-strength tablet formulation (G012) (Treatment Arm C, Cohort 2C). Relative BA of the FDC2 regular-strength tablet will be assessed by comparing the PK results from Cohort 2C to Cohort 1A.

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

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

Subjects will be randomly assigned to 1 of 2 treatment arms in Cohort 1 which include Treatments A and B as shown in Table 5. Subjects will be assigned to Treatment C in Cohort 2 and Treatment D or E in Cohort 3 (based on the interim analysis results for Cohort 1).

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

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

Table 5: Study Cohorts and Treatments

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

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

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

[b] Subjects continue treatment until disease progression, withdrawal of consent, loss to follow-up, lack of clinical benefit in the opinion of the investigator, or sponsor ends the study.

[c] Modified fasting defined as study drug intake on empty stomach only: intake at least 1 hour before or at least 2 hours after a meal.

[d] Subjects will receive niraparib + AA or AA alone QD, each in combination with 5 mg prednisone (or prednisolone) BID, during the Extension Phase at the investigator's discretion guided by HRR gene alteration status.

Cohort 2 will test the FDC 2 regular-strength (G012) tablet formulation. Cohort 3 will test 1 of the 2 low-strength FDC tablet formulations (FDC 1 [G009] or FDC2 [G014]).

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

After completion of the PK Assessment Phase, subjects will enter the Extension Phase to receive treatment with either niraparib 200 mg once daily plus AA 1,000 mg once daily (both as SAs) and

prednisone/prednisolone 5 mg twice daily or AA 1,000 mg once daily and prednisone/prednisolone 5 mg twice daily; treatment cycles are 28 days.

Treatment will continue until discontinuation for disease progression, unacceptable toxicity, withdrawal of consent, loss to follow up, lack of clinical benefit in the opinion of the investigator, start of subsequent anticancer therapy, or the Sponsor ends the study.

1.3. Statistical Hypotheses for Trial Objectives

1.3.1. Combination 1: Niraparib and Cetrelimab

The hypotheses for this combination are:

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

1.3.2. Combination 2: Niraparib and AAP

The hypotheses for this combination is:

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

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

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

1.4. Sample Size Justification

1.4.1. Combination 1: Niraparib and Cetrelimab

For Part 1 of the study, at least 6 evaluable subjects will initially be enrolled. Additional dose regimens may be enrolled and non-evaluable subjects will be replaced.

For part 2 of study, approximately 30 subjects per cohort (i.e., Cohort 1A=BM+ or Cohort 1B=BM-) were to be enrolled. However, a futility analysis was performed for Cohort 1B after approximately 10 subjects have been enrolled and evaluated, the analysis result showed that a response rate of 13% was not achieved. It is anticipated that the final analysis for the primary

endpoint of ORR will occur approximately 6 months after the last subject in each cohort is enrolled. Note that Cohorts 1A and 1B will be evaluated and analyzed independently.

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

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

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

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

1.4.2. Combination 2: Niraparib and AAP

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

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

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

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

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

Based on the study data under single dose condition (212082PCR1007/abiraterone and TESARO-GSK 3000-01-004 Tablet Pilot BA/Niraparib), a sample size of 30 PK evaluable subjects (15 per arm) will provide the point estimates of the GMRs between JNJ-64091742 (niraparib) Clinical Protocol 64091742PCR2002 and reference with following precisions (see Table 6). All subjects who have at least 1 noncompartmental PK parameter estimated will be considered PK evaluable.

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

Table 6: Precisions of the point estimates for GMR

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

1.5. Randomization and Blinding

1.5.1. Randomization

For Combination 1 and 2, no blinding or randomization procedures will be performed.

For Combination 3, randomization will be used in Cohort 1 between Treatment Arms A and B only to avoid bias in the assignment of subjects to treatment sequence groups, to increase the likelihood that known and unknown patient attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment sequence groups, and to enhance the validity of statistical comparisons across the groups. Approximately 34 subjects (17 subjects per arm) will be enrolled into Cohort 1 of the study (2 parallel treatment arms). As subjects qualify for the study,

they will be assigned a subject randomization number in strict sequential order. Based on a computer-generated randomization schedule prepared under the sponsor's supervision before the start of the study, subjects will be randomly assigned to receive the treatments in 1 of 2 possible treatment groups (A, B). Assignment to treatment group will occur before a subject receives the study drug. Subjects who drop out during the PK assessment phase may be replaced to assure at least 30 subjects complete Cohort 1. Subjects who are replaced during the PK Assessment Phase may continue to the Extension Phase.

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

1.5.2. Blinding

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

2. GENERAL ANALYSIS DEFINITIONS

Study Day is calculated in reference to the date of first dose. Positive study days will count forward from Study Day 1. Study Day -1 will be the day before Study Day 1, and all subsequent negative study days will be measured backward from Study Day -1. There will be no Study Day 0.

For Combinations 1 and 2, the first dose starts on Day 1 of Cycle 1. For Combination 3, the first dose starts on Day 1 of the PK week. Unless otherwise specified, baseline value is defined as the closest measurement prior to or on the date of the first dose of study drug. Change from baseline will be defined as (post-baseline value – baseline value).

Treatment Duration is calculated as the duration of time from the date of the first dose of study drug to the date of last dose of the study drug, ie, date of last dose – date of first dose + 1.

Time to Event is calculated as the number of days from the date of enrollment to the date of the event of interest, i.e., date of event of interest – date of enrollment + 1. Time to event or duration of event endpoints will be based on the actual date of the event, not visit number or visit date.

Continuous/numerical variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using count and percentage.

Missing data will be handled using data as observed approach, no imputation will be implemented unless specified.

Summary tables of study disposition, treatment disposition, study compliance, treatment-emergent adverse events (TEAE), and death will include COVID-19 related missing information to assess potential impacts on the data analysis.

2.1. Pooling Algorithm for Analysis Centers

There is no plan to pool the centers (study sites) for analyses.

2.2. Analysis Sets

2.2.1. Intent-to-Treat Analysis Set

Intent-to-Treat (ITT) is the efficacy analysis set. It includes all subjects who were enrolled into the study and had at least 1 dose of both study drugs at the selected RP2D in part 2 of study.

2.2.2. Safety Analysis Set

The safety analysis set includes all subjects who received at least 1 dose of study drug. It will be used for evaluating safety and treatment compliance.

2.2.3. Pharmacokinetics Analysis Set

All subjects who received at least 1 dose of both study drugs and have at least 1 concentration value. PK population is for Combination 1 only.

2.3. Definition of Subgroups

Since both Combination 1 and 2 have been closed to enrollment early with fewer subjects available, no planned subgroup analysis will be performed.

3. INTERIM ANALYSIS AND DATA REVIEW COMMITTEE

3.1. Data Review Committee (DRC)

This does not apply to Combination 3.

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

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

3.2. Futility Analysis

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

The pre-planned futility analysis was performed on the biomarker negative subjects (Cohort 1B). Based on the analysis conducted, a response rate of 13% was not achieved. Accordingly, the

biomarker negative cohort (Cohort 1B) was closed to new enrollment. Subjects that were enrolled in this cohort and still on study may continue without any change to their status.

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

4. SUBJECT INFORMATION

The analyses described in Section 4 will be performed separately for all 3 combinations.

The number of subjects in each analysis set will be summarized. In addition, the distribution of subjects by site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 7 presents a list of the demographic and baseline characteristics variables that will be summarized by cohorts and overall for the safety analysis set for each combination.

Table 7: Demographic Baseline Characteristics Variables

Continuous Variables:	**Summary Type**
• Age (years) • Weight (kg) • Height (cm) • Baseline PSA value, hemoglobin, CTC, platelet, neutrophil, lactate dehydrogenase, alkaline phosphatase value • Time from Initial Diagnosis to Day 1 Cycle 1	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Categorical Variables	
• Age <65 years, ≥65 to 69 years, ≥70 to 74 years, ≥ 75 years • Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple) • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Baseline ECOG performance status (0, 1, 2) • Gleason score at study entry • Extent of disease progression (Bone, Visceral,…) • Evidence of disease progression at study entry • Number of prior therapies (Number of AR-targeted, taxane, cytotoxic chemotherapy, and other therapy)	Frequency distribution with the number and percentage of subjects in each category.

[a]If multiple race categories are indicated, the race is recorded as 'Multiple' Note that collection of race and ethnicity is limited to countries were permitted.

4.2. Disposition Information

The number and percentage of subjects who are enrolled, dosed, treatment discontinuation and study discontinuation (including reasons) will be summarized using the safety analysis set analysis set.

4.3. Treatment Compliance

Treatment compliance and dose modifications will be summarized using the safety analysis set.

Subjects receive the scheduled dose as per protocol specification during the treatment phase, unless the subjects experienced toxicity that resulted in protocol-specified dosing modifications.

Treatment compliance will be summarized descriptively and will be calculated as ratio of actual dose intensity/planned dose intensity *100%. Dose intensity is defined as the total amount of drug given in a fixed unit of time. Treatment compliance will also include assessment of dose interruption and reasons for dose modification.

4.4. Study Procedures

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

For each subject, the planned maximum amount of blood drawn will not exceed 70 mL at any visit. Refer to the study Laboratory Manual for details regarding blood volumes to be collected for each visit.

4.4.1 Prescreening Phase for Biomarker Evaluation

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

4.4.1.1 Combination 1: Niraparib and Cetrelimab

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

4.4.1.2 Combination 2: Niraparib and AAP

For Combination 2, subjects will be eligible to proceed to the Screening Phase if determined to have DRD.

4.4.1.3 Combination 3: Niraparib/Abiraterone Acetate Fixed-dose Combination Tablet

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

4.4.2 Treatment Phase

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

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

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

4.4.3 End-of-Treatment Visit

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

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

4.4.4 Follow-Up Phase

Once a subject has completed the Treatment Phase, deaths regardless of causality and SAEs thought to be related to study drugs, including associated concomitant medications, will be collected and reported within 24 hours of discovery or notification of the event. Related AEs should be reported as per the procedures in Section 12.3.1. If the follow-up information is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents.

Once a subject has completed the Treatment Phase for a reason other than radiographic progression, CT, MRI, or bone scans (^{99m}Tc) will be collected every 3 months (±2 weeks) until confirmed radiographic progression or initiation of subsequent therapy, provided the subject does not withdraw consent. If a subject has documented radiographic progression during the Treatment Phase, additional radiographic assessments are not required during the Follow-up Phase.

4.5. Extent of Exposure

Extent of exposure will be summarized using the safety analysis set in terms of treatment duration in cycles and in months, which are calculated as the number of days with dosing record divided by 30.4375 (ie, number of days in a month calculated as 365.25/12).

4.6. Protocol Deviations

Major protocol deviations will be summarized using the safety analysis set. Protocol deviations will be reviewed on a case-by-case basis and assessed if they are considered major protocol deviations. The final list will be compiled prior to database lock. Examples of major protocol deviations may include, but are not limited to, the following categories:

- Deviation from inclusion/exclusion criteria
- Major study drug dosing errors or dose modifications that are not within the protocol specifications that may compromise subject safety or efficacy assessments.
- Administration of prohibited concomitant medication during the course of the study treatment period
- Any other deviation that impacts subject safety

4.7. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by World Health Organization (WHO) Drug Therapeutic Class and generic medication name using the safety analysis set. Prior medications are those taken (with medication start date) prior to Cycle 1 Day 1. Concomitant medications are those, other than study drug, taken during the Treatment Phase.

Subsequent prostate cancer therapies received after the Treatment Phase will be summarized using the safety analyses set. If the therapy is medication, then it will also be summarized by WHO Drug Therapeutic Class and generic medication name.

5. EFFICACY

The following efficacy analyses will be performed separately for Combination 1 and 2.

A summary of the planned analyses for efficacy endpoints are listed in Table 8 and 9, more details can be found in subsequent sections.

Table 8: Planned Analyses for Efficacy Endpoints, Combination 1

Endpoint		**Analysis Method**
Primary endpoint	Objective response rate (ORR)	• Descriptive summary • Two-sided 90% exact confidence interval
Secondary endpoint	Composite Response Rate as defined in Section 1.1	• Descriptive summary • Two-sided 90% exact confidence interval
	CTC response rate	• Descriptive summaries • Two-sided 90% exact confidence interval
Exploratory endpoints	Change from baseline in CTC counts over time	• Descriptive summaries over time • Longitudinal plot

Table 9: Planned Analyses for Efficacy Endpoints, Combination 2

Endpoint		**Analysis Method**
Primary endpoint	Composite Response Rate as defined in Section 1.1	• Descriptive summary • Two-sided 90% exact confidence interval
Secondary endpoint	Objective response rate (ORR)	• Descriptive summary • Two-sided 90% exact confidence interval
	CTC response rate	• Descriptive summaries • Two-sided 90% exact confidence interval
Exploratory endpoints	Change from baseline in CTC counts over time	• Descriptive summaries over time • Longitudinal plot

5.1. Analysis Specifications

5.1.1. Level of Significance

In general, all confidence intervals will be calculated on the two-sided 90% confidence level (CI), unless otherwise specified.

5.1.2. Data Handling Rules

In general, no imputation method is planned for handling missing or incomplete data unless specified otherwise. Sensitivity analyses with censoring rules may be conducted if warranted and will be documented in the clinical study report.

The following imputation rule will be used for missing dates in the assessment of an event:

Partial event onset dates will be imputed as follows:

- If the onset date of an event is missing day only, it will be set to:
  - First day of the month that the event occurred, if month/year of the onset of event is different than the month/year of the Day 1
  - The day of Day 1, if the month/year of the onset of AE is the same as month/year of the Day 1 and month/year of the event resolution date is different
  - The day of Day 1 or day of event resolution date, whichever is earliest, if month/year of the onset of event and month/year of the Day 1 and month/year of the event resolution date are same
- If the onset date of an event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the Day 1
  - Month and day of the Day 1, if this date is the same year that the event occurred
  - Last day of the year if the year of the event onset is prior to the year of the Day 1,
  - The event resolution date.
- Completely missing onset dates will not be imputed.

Partial event resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

Combination 1

The primary endpoint is objective response rate (ORR), defined as the proportion of subjects with measurable disease whose best response is either complete response (CR) or partial response (PR) as defined by RECIST 1.1[2] with no evidence of bone progression according to the PCWG3 criteria[3].

The primary efficacy analysis is performed on the ITT population. The estimand, rate of objective response, will be estimated using the number of subjects who achieve CR/PR and no evidence of bone progression divided by the number of subjects in the ITT population. It will be summarized by cohort, and no comparison will be made between cohorts.

Combination 2

The primary endpoint is composite response rate, defined as the proportion of subjects who have composite response. A composite response exists when a response is seen in 1 of the following by PCWG3 criteria[3]:

- Objective response (confirmed per RECIST 1.1[2]), or
- CTC response: defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC ⩾1 at baseline or CTC<5 per 7.5 mL with CTC ⩾5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later, or
- PSA decline of ⩾50%, measured twice 3 to 4 weeks apart.

Primary efficacy analysis is performed on the ITT population. The estimand, RR, will be estimated using the number of subjects who have composite response divided by the number of subjects in the ITT population. It will be summarized by cohort, and no comparison will be made between cohorts.

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following four components:

- Population: ITT analysis set;
- Variable: ORR/RR;
- Intercurrent events and strategies:

Missing baseline assessment	Assume non-response
No post baseline response assessment	Assume non-response

- Population-level summary: ORR/RR will be summarized along with 90% 2-sided exact CI.

5.2.3. Analysis Methods

Analysis will be performed separately for each combination.

ORR/RR final analysis will be performed approximately 6 months after the last subject receives study medication. ORR/RR will be analyzed and considered as the primary analysis for Combination 1/2.

All enrolled subjects with measurable disease as defined by RECIST 1.1[2] will be analyzed for objective response. Subjects who discontinue the study drug without response assessment will be considered as non-responders in the analysis. The ORR/RR will be calculated and its 2-sided 90% exact CI will be presented. In addition, the number and percentage of subjects in each response category (CR, PR, etc.) will be tabulated.

5.3. Secondary Endpoints

Secondary endpoints include CTC response rate and duration of objective response for both Combination 1 and 2, RR for Combination 1, ORR for Combination 2.

5.3.1. Definition

The CTC response rate is defined as the proportion of subjects with CTC response. CTC response is defined as CTC=0 per 7.5 mL of blood at 8 weeks for subjects who have CTC $\geqslant$1 at baseline or CTC<5 per 7.5 mL with CTC $\geqslant$5 at baseline, confirmed by a second consecutive value obtained 4 or more weeks later. Enrolled subjects with no CTC assessment at baseline or at week 8 will be classified as non-responders.

The Duration of objective response is defined as the time from complete response or partial response to radiographic progression of disease, unequivocal clinical progression or death, whichever occurs first.

5.3.2. Analysis Methods

The Following analyses on CTC response will be performed for ITT population:

- Descriptive summaries
- CTC response rate will be tabulated and its 2-sided 90% exact CI
- Waterfall plots of percent change in CTC will also be presented.

All time-to-event secondary endpoints will be evaluated using Kaplan-Meier method for ITT analysis set. Median time to event and the corresponding 90% CI will be provided. Descriptive summaries will be provided for ITT analysis set. In addition, waterfall plots for PSA will be presented for to demonstrate the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximal decline in PSA.

6. SAFETY

The safety analyses will be carried out separately for each combination.

The safety parameters to be evaluated are the incidence, intensity, and type of adverse events (AE), vital signs, ECG, and clinical laboratory results.

Unless otherwise specified, no inferential statistical analyses will be performed in analyzing the safety data.

6.1. Adverse Events

Subjects will be assessed for adverse events at each monthly clinic visit while on the study. Adverse events (AEs) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03[1] or later and coded to preferred term and system organ class (SOC) using the MedDRA version 18.0 or later.

All AEs reported on or after the date of first dose, until 100 days after the last dose of study drugs for Combination 1 and 30 days for Combinations 2 and 3, will be considered treatment-emergent and will be summarized.

AE incidence rates will be summarized with frequency and percentage by SOC and preferred term, with all subjects treated as the denominator, unless otherwise specified. In addition, AE incidence rates will also be summarized by severity and relationship to study drug. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the study drug. Subjects with multiple occurrences of events will only be counted once at the maximum severity level to study drug for each preferred team, SOC, and overall. Deaths that occur within 30 days after the last dose of study drug are defined as on-study deaths.

Summary tables of the following AEs will be provided:

- Overall summary of AEs: the number and percentage of subjects who experienced any AE, number of subjects with Grade 3/4 AEs, any serious adverse event (SAE), any treatment-related AE, any treatment-related SAE, AE leading to treatment discontinuation, AE leading to death, and all deaths within 30 days of last dose
- Most frequent AEs by SOC and preferred term (reported in ≥ 5% of subjects)
- All AEs by SOC, preferred term, and toxicity grade
- Grades 3 or 4 AEs by SOC and preferred term
- Treatment-related AEs by SOC, preferred term, and toxicity grade
- Most frequent treatment-related Grades 3 and 4 AEs (reported in ≥ 5% of subjects)
- All AEs that led to death by SOC and preferred term
- All AEs that led to study drug discontinuation by SOC and preferred term. Study drug discontinuation will be determined from the End of Treatment CRF (where reason for termination is "Adverse Event") and the specific AE will be determined from the AE eCRF page (where action taken is "Withdrawn from Study")
- All AEs that led to study drug discontinuation by SOC, preferred term, and toxicity grade
- All AEs that lead to study drug dose modification by SOC and preferred term
- All SAEs by SOC and preferred term
- All SAEs by SOC, preferred term, and toxicity grade
- Deaths by time period (Treatment Phase, Follow-up Phase) and cause of death

Subject listings of all Grades 3 or 4 AEs, all SAEs, AEs that led to study drug discontinuation, dose modification, and all deaths will be provided as well.

Narratives will be written to include the following subjects in the final clinical study report:

- Subjects who die within 30 days of the last dose of study drug
- Subjects who discontinue study drug due to adverse events

- Subjects who have a treatment-related serious adverse event
- Subjects who have a Grade 3 or higher treatment-emergent adverse events of special interest

6.2. Clinical Laboratory Tests

For continuous/numerical measurements, descriptive statistics will be provided at baseline and for observed values and changes from baseline at each scheduled time point. The number and percentage of subjects with abnormal laboratory values will be summarized. The number and percentage of subjects whose NCI-CTCAE (version 4.03[1] or later) toxicity grades of ≥ 3 will also be summarized. For selected key laboratory measurements, changes in toxicity grade from baseline to the worst grade experienced by the subject during the Treatment Phase and the Study will be summarized using shift tables.

A listing of subjects who develop toxicities of Grade ≥ 3 will be provided for each laboratory parameter.

6.3. Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic) and body weight values and changes from baseline will be summarized at each scheduled time point. Descriptive statistics of other vital signs (body temperature, heart rate, respiratory rate) at baseline will also be summarized.

Baseline vital signs, blood pressure (systolic and diastolic), and heart rate will be summarized. Only blood pressure and heart rate are reported during the treatment phase. Subjects with markedly abnormalities in blood pressure as compared to baseline will be summarized according to the following table.

Table 10: Criteria for Markedly Abnormality Subjects

Parameter	Criteria for Markedly Abnormality
Systolic Blood Pressure	Absolute result < 90 mmHg and decrease from baseline > 20 mmHg
	Absolute result > 160 mmHg and increase from baseline > 20 mmHg
Diastolic Blood Pressure	Absolute result < 50 mmHg and decrease from baseline > 10 mmHg
	Absolute result > 100 mmHg and increase from baseline > 10 mmHg
Weight	10 - < 20% weight loss from baseline

6.4. Physical Examination

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

6.5. Electrocardiogram

Electrocardiogram parameters will be summarized using descriptive statistics. The number and percentage of subjects with values beyond clinically important limits will also be summarized.

PK analyses will be performed on the PK analysis set, and will be conducted and reported separately.

7. MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Data collected on medical resource utilization (MRU) will be used in the construction of economic model. The modeling and reporting will be provided in a separate report.

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3. Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402-1418.