Title: Phase 1/2a Dose-Escalation and Expansion Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of CORT125281 with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer

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STATISTICAL ANALYSIS PLAN (SAP)

Title	
Study Protocol	CORT125281-601
Phase	1/2a
Investigational Product	Exicorilant (CORT125281)
Indication	Metastatic Castration-Resistant Prostate Cancer
Protocol Version	Amendment 5
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Confidentiality Statement

APPROVAL SHEET

STATISTICAL ANALYSIS PLAN

SAP for Protocol: CORT125281-601
SAP Version / Date: V1.0 / [16 March 2022]
Reviewed and Approved at Corcept Therapeutics Incorporated by:

[redacted]

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List of Abbreviations

Abbreviation	Definition
λ_z	terminal elimination rate constant
Abi	abiraterone
AE	adverse event
ACTH	adrenocorticotrophic hormone
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
ARant	androgen-receptor antagonist
ARV7	androgen-receptor splice variant 7 messenger RNA
AUC	area under the curve
AUC0-24	area under the curve from 0 to 24 hours
AUC0-6	area under the curve from 0 to 6 hours
AUC0-inf	area under the curve from 0 to infinity
AUC0-last	area under the curve from 0 to time of last measurable concentration
BID	twice daily
CI	confidence interval
Cmax	maximum observed plasma concentration
Cmin	minimum concentration
CRPC	castration-resistant prostate cancer
CR	complete response
CTC	circulating tumor cell
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DRC	Data Review Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End-of-Treatment
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GC	glucocorticoid
GCP	Good Clinical Practice
GR	glucocorticoid receptor
HIV	human immunodeficiency virus
HR	hazard ratio
ICH	International Council for Harmonisation

ICF	informed consent form
IHC	immunohistochemistry
LDH	lactic dehydrogenase
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
ORR	objective response rate
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	once daily
QoL	quality of life
RP2D	recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAE	serious adverse event
SoA	Schedule of Assessments
SOC	system organ class
SOP	Standard Operating Procedure
SSE	symptomatic skeletal event
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
Tlast	time after dosing of the last quantifiable concentration
UFC	urinary free cortisol
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WHODD	WHO Drug Dictionary

1. Introduction

1.1. Background

Prostate cancer growth, driven by androgens, routinely involves androgen deprivation therapy with gonadotropin-releasing hormone analogues for patients with locally advanced or metastatic prostate cancer. Approved hormone-based therapies such as abiraterone, which inhibits androgen synthesis, and enzalutamide, an androgen receptor (AR) antagonist, have demonstrated a survival advantage in both post-docetaxel as well as chemotherapy-naïve patients. In patients with castration-resistant prostate cancer (CRPC) treated with anti-androgen therapy, the glucocorticoid receptor (GR) can become the dominant growth factor and provides a mechanism of resistance to drugs such as enzalutamide. The present study hypothesizes that treatment with a GR antagonist in combination with enzalutamide will overcome a mechanism of resistance to androgen-targeted therapies, and thereby provide clinical benefit to patients with metastatic CRPC (mCRPC), compared with enzalutamide alone, as well as to patients who have developed enzalutamide resistance.

CORT125281 (International nonproprietary name: exicorilant, which will be used throughout the statistical analysis plan (SAP) instead of CORT125281), a selective GR modulator, is being developed for treatment of mCRPC.

CORT125281-601 is a Phase 1/2a, dose-determination and expansion study conducted in patients with mCRPC to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of exicorilant in combination with enzalutamide. The primary objective of this study is to determine the maximum tolerated dose (MTD) and/or biologically active doses of exicorilant in combination with enzalutamide and to identify the recommended Phase 2 dose (RP2D).

Details of the analyses required to address study objectives are presented in this Statistical Analysis Plan (SAP). This SAP has been developed and will be approved prior to data unblinding and data analysis. All analyses supporting the clinical study report (CSR) will be conducted after clinical trial data are entered into the database, discrepancies resolved, and the database is authorized (closed to further changes). Any deviations from the SAP will be documented as such in the study report. Additional exploratory biomarker analyses of these and other assessments may be conducted and described in a separate Biomarker SAP.

Production and quality control of statistical analyses and accompanying tables, listings, and figures (TLFs) will be the responsibility of [redacted] with appropriate oversight by Corcept Therapeutics Biometrics team.

1.2. Protocol and Amendment History

This SAP is based on Amendment 5 of Protocol CORT125821-601, which incorporates the following Amendments:

Version	Approval Date	Major Changes, if any*
Protocol	16 August 2017	
Amendment 1	29 September 2017	Modified the definition of DLTs
Amendment 2	19 December 2017	Updated entry criteria, clarified the definition of MTD and clarified performing AE assessments and SAE reporting
Amendment 3	09 January 2018	Added additional date from Phase 1 study, clarified dosing schema, added requirement for sentinel dosing, revised the Section of Statistical Methods
Amendment 4	25 July 2018	Modified entry criteria and clarified QOL collections
Amendment 5	21 February 2020	Study design updated to include segment 2 of randomized double-blind portion, under once daily fed conditions
* Changes expected to require accommodation in analysis plan.		

2. Study Design

2.1. Design Overview

This is a Phase 1/2a dose-determination and expansion study conducted in patients with mCRPC to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of exicorilant in combination with enzalutamide; and to identify the RP2D. This open-label study consists of 2 phases: a Dose-Determination Phase (Phase 1) and an Expansion Phase (Phase 2a). The Dose-Determination Phase is made up of 2 segments: Segment 1 (an open-label, twice daily exicorilant) and Segment 2-double-blind, once daily exicorilant under fed conditions). Figure 1 shows the overall schematic for the study design.

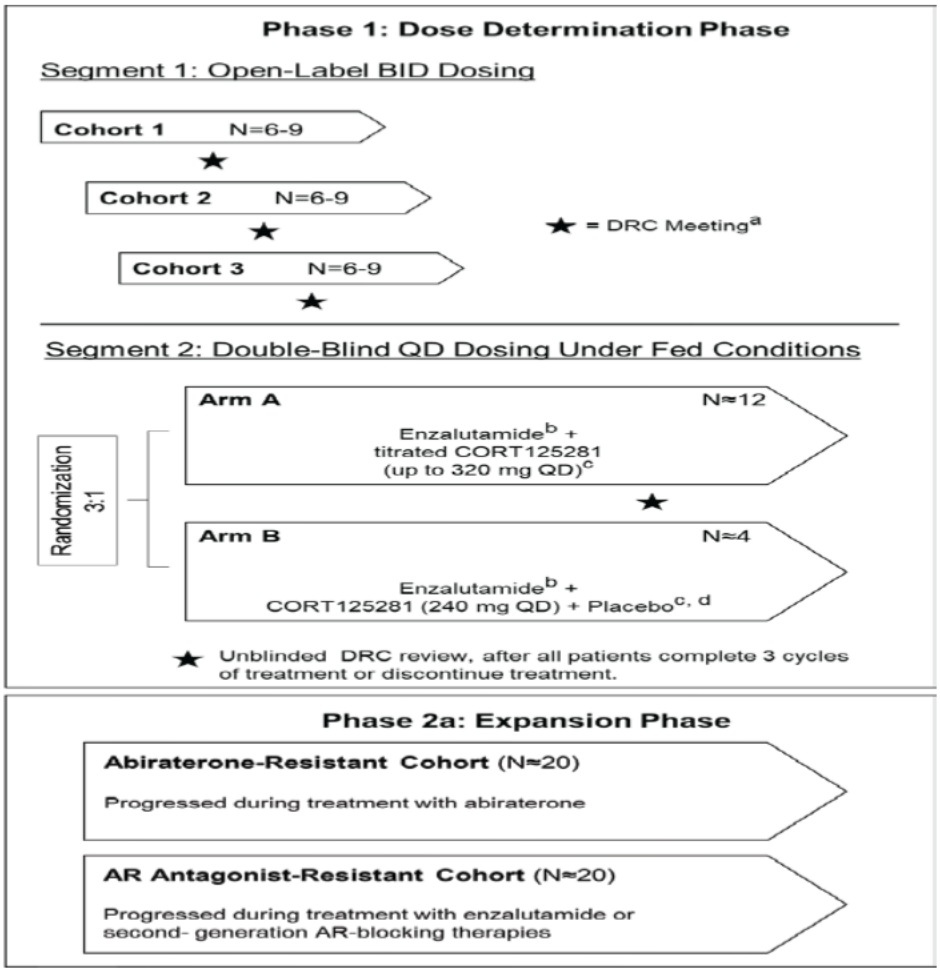
Patients will participate in the following study periods:

- Screening Period will take place within 28 days before the first dose of study treatment
- Lead-In Period:

  - Dose-Determination Phase Segment 1: Enzalutamide monotherapy for 28 days was planned. This may be updated per Data Review Committee (DRC) data review.
  - Dose-Determination Phase Segment 2: No Lead-In Period is planned.
  - Expansion Phase:
    - Food-Effect Subcohort: A single dose of exicorilant under fasting conditions on Cycle 1 Day -7, and a single dose of exicorilant 30 minutes after a standard breakfast on Cycle 1 Day 1
    - Non-Food-Effect Patients: No Lead-In Period

- Combination Treatment Period: Patients will take combination treatment (exicorilant and enzalutamide) until reaching disease progression, experiencing unmanageable toxicity, or until other treatment discontinuation criteria are met. Patients will continue assessments per the Schedule of Assessments (SoA) for the Combination Treatment Period until both exicorilant and enzalutamide are discontinued.
- Follow-Up Period: Patients will return for a Post-Treatment Follow-Up Visit (End-of-Treatment +30 Days Visit) 30 days after their final dose of exicorilant or enzalutamide, whichever is later. After this, patients will continue to be followed for progression, information on subsequent anticancer therapies (start and end date and response) and survival.

Figure 1: CORT125281-601 Phase 1/2a Schematic



AR, androgen receptor; BID, twice daily; DLT, dose-limiting toxicity; DRC, Data Review Committee; MTD, maximum tolerated dose; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily.

[a] The DRC will review the safety, PK, and PD data from Dose-Determination Segment 1 once a minimum of 3 evaluable patients have completed the DLT-evaluation period (Protocol Section 5.4.1).

[b] Enzalutamide will be continued at the dose currently tolerated by the patient at the time of Screening.

[c] The investigational agent will be increased in 40-mg increments every 2 weeks, as tolerated, with either exicorilant to a maximum dose of 320 mg QD under fed conditions (Arm A) or with placebo (Arm B) to maintain a exicorilant dose of 240 mg QD under fed conditions (Table 1).

[d] After the DRC meeting for Dose-Determination Segment 2 and determination of the Phase 2 RD, patients initially randomized to Arm B will have their exicorilant dose escalated per the recommended Phase 2 regimen.

2.2. Phase 1, Dose-Determination Segment 1 (Open-Label)

Segment 1 of the Dose-Determination Phase is designed to determine dose limiting toxicity (DLTs), the MTD/biologically active doses and the RP2D of exicorilant + enzalutamide in patients with mCRPC. Each cohort must include a minimum of 3 evaluable patients, but can enroll up to 9 patients for dose optimization and selection of the RP2D. The DRC may make the recommendation to adjust the size of a cohort to more than 9 patients to further evaluate a given dose (eg, based on PK data or tolerability). A minimum of 3 evaluable patients in each cohort must complete 28 days of continuous combination treatment with enzalutamide and exicorilant and have safety data reviewed by the DRC prior to proceeding to the next dose level. If <33% of the DLT-evaluable patients have experienced a DLT (see Protocol Section 5.5 for definition), then enrollment may proceed in the next cohort. If ≥33% of the DLT-evaluable patients have experienced a DLT in a cohort, then recruitment to that cohort will be discontinued, and this dose will be determined to be not tolerated. Dose escalation of exicorilant will initially be in up to doubling steps until any DLT or Grade 2 toxicity attributed to exicorilant is reported; thereafter, dose escalation will be in ≤50% steps. The starting dose for the subsequent cohort will be per the DRC recommendation and will be based upon tolerability and observed toxicity in previous cohorts (including DLTs), human PK, PD markers of target engagement, projected efficacious exposures, and the available capsule strengths. The DRC may adjust the dose of enzalutamide in subsequent cohorts based on PK and tolerability.

2.3. Phase 1, Dose-Determination Segment 2 (Double-Blind)

Segment 2 of the Dose-Determination Phase is randomized and double blinded for dose titration with respect to exicorilant in combination with enzalutamide. All patients will receive exicorilant at a starting dose of 240 mg once daily (QD) under fed conditions. Approximately 20 patients will be enrolled to achieve 16 DLT-evaluable patients randomized in a 3:1 ratio to receive exicorilant in combination with enzalutamide either with the starting dose of exicorilant 240 mg QD with dose titration to 320 mg QD (N=12; Arm A) or with the starting dose of exicorilant 240 mg QD, without an increase of the active dose (N=4; Arm B). Patients in Arm B will receive placebo capsules, such that the patient, Investigators, and study team are blinded to which dose patients are receiving (ie, 240 mg QD versus 240 mg to 320 mg QD). In Segment 2, all doses of exicorilant should be taken with food.

All patients will start treatment with exicorilant 240 mg QD on Cycle 1 Day 1. Patients will continue on their current dose of enzalutamide during the Screening Period and at the initiation of exicorilant. Beginning on Cycle 1 Day 16, the dose of exicorilant will be increased in 40-mg increments every 2 weeks, as tolerated, with either exicorilant (Arm A; N=12) to a maximum dose of exicorilant 320 mg QD or with placebo (Arm B; N=4) (Table 1). If any planned dose escalation is postponed due to transient intolerable Grade 2 toxicity or scheduling conflicts (delays in escalation

not due to toxicity), the dose may be escalated within 14 days of the planned escalation.

- **Arm A (N=12)**: exicorilant 240 mg QD under fed conditions with upward dose titration in combination with enzalutamide. Exicorilant will be increased in 40-mg increments every 2 weeks (+14-day window) based upon tolerability to a maximum dose of 320 mg QD (Table 1).

  –Cycle 1 Day 1: exicorilant 240 mg QD
  –Cycle 1 Day 16 (+14-day window): exicorilant 280 mg QD
  –Cycle 2 Day 2 to Cycle 2 Day 16 (+14-day window): exicorilant 320 mg QD

- **Arm B (N=4)**: exicorilant 240 mg QD under fed conditions, with an increase in the number of placebo capsules every 2 weeks (+14-day window) (Table 1).

  –Cycle 1 Day 1: exicorilant 240 mg QD
  –Cycle 1 Day 16 (+14-day window): exicorilant 240 mg QD
  –Cycle 2 Day 2 to Cycle 2 Day 16 (+14-day window): exicorilant 240 mg QD

Table 1: Exicorilant Upward Dose Titration for Dose-Determination Segment 2

Dose Level	Resulting exicorilant Dosage (QD)		Open-Label Bottle (exicorilant)	Blind-Label Bottle (exicorilant or Placebo)[a]
	Arm A	Arm B		
1 (Starting Dose)	240 mg	240 mg	6 capsules	0 capsules
+1 (First Increase)	280 mg	240 mg	6 capsules	1 capsule
+2 (Second Increase)	320 mg	240 mg	6 capsules	2 capsules

QD, once daily.
Note: The exicorilant dosage will be escalated in 2-week intervals unless there are intolerable Grade 2 toxicities, dose-limiting toxicities, or Grade 3 or greater toxicities attributed to exicorilant (Protocol Section 5.7).
a. Note: The blind-label bottle contains blinded capsules (exicorilant [Arm A] or placebo [Arm B]).

During the double-blind portion of the Dose-Determination Phase (ie, Segment 2), an unblinded Medical Monitor independent of the study team will provide additional oversight for the study, including review of serious unexpected adverse events (AEs) considered related to either exicorilant or enzalutamide and DLTs.

After all patients complete 3 cycles of treatment or discontinue treatment, the data will be unblinded and the DRC will meet to review the safety and available PK and PD data. The DRC will evaluate the frequency of DLTs, the DLT rate (the number of DLTs per week [7-day period] during the DLT-evaluation period), and overall tolerability in their assessment of the dose titration regimen as the Phase 2 RP2D. If the DLT rate for the regimen is ≥33%, alternative titration schemes may be considered as the regimen for the RP2D, such as greater time increments between dose escalations or limiting the upper range of the regimen to those dose levels corresponding to a DLT rate of <33%. Once the DRC has determined the RP2D,

patients assigned to Arm B who have not experienced dose reductions due to toxicity will have their exicorilant dose escalated per the recommended Phase 2 regimen.

2.4. Phase 2a, Expansion Phase

Once the RP2D has been determined in the Dose-Determination Phase, the following cohorts will be enrolled and treated with exicorilant + enzalutamide according to the RP2D regimen. The DRC may elect to expand more than 1 dose level, if needed, to better define the RP2D.

- **Abiraterone (Abi)-Resistant Cohort:** Patients who have progressed during treatment with abiraterone and have received no other AR-blocking therapies (N≈20)
  - Food-Effect Subcohort: The effect of food on the PK of exicorilant will be evaluated in 10 patients enrolled to the Abi-Resistant Cohort. These 10 patients will have a 7-day Lead-In Period as follows:

    Day -7: Single oral dose of exicorilant administered under fasting conditions.
    Day 1: Single oral dose of exicorilant administered 30 minutes after a standard breakfast. These patients will initiate enzalutamide on Cycle 1 Day 2 to avoid confounding the assessment of the effect of food on exicorilant PK.

    Patients in the Abi-Resistant Cohort who do not participate in the food-effect study will not have a Lead-In Period.
- **AR Antagonist (ARant)-Resistant Cohort:** Patients who have progressed during treatment with enzalutamide or second-generation AR-blocking therapies (N≈20). Note: Patients in the ARant-Resistant Cohort will not have a Lead-In Period.

3. Study Objectives

3.1. Primary Objective

The primary objective of this study is to determine the MTD and/or biologically active doses of exicorilant in combination with enzalutamide to identify the recommended dose for Phase 2 studies (RP2D).

3.2. Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the safety and tolerability of exicorilant in combination with enzalutamide.
- Characterize the preliminary efficacy of exicorilant in combination with enzalutamide by determining the objective response rate (ORR), proportion of patients with a reduction in prostate-specific antigen (PSA) level by >50%, time to a symptomatic skeletal event (SSE), radiographic progression-free survival (rPFS), including the

proportion of patients who are progression-free at 4, 6, and 12 months, duration of response (DOR), and overall survival (OS).
- Assess time to biochemical (PSA progression) bone disease progression, and clinical progression, including the proportion of patients who are progression-free at 4, 6, and 12 months.
- Determine the PK profile of exicorilant and enzalutamide, when co-administered.
- Determine the effect of food on the PK of exicorilant.

3.3. Exploratory Objectives

Exploratory objectives of this study are to:

- Evaluate the effects of exicorilant in combination with enzalutamide on the hypothalamic pituitary-adrenal (HPA) axis, including assessments of:
  - Urinary free cortisol (UFC)
  - Serum cortisol
  - Plasma adrenocorticotrophic hormone (ACTH)
- Explore the antitumor activity of the combination of exicorilant and enzalutamide by line of therapy and in specific sub-sets of disease, including:
  - GR+ vs. GR-, by tumor immunohistochemistry (IHC) and/or circulating tumor cells (CTCs)
  - Androgen-receptor splice variant 7 messenger RNA (ARV7) status
  - Systemic antagonism of cortisol activity as assessed by whole blood transcriptional profiling
- Assess change in PSA.
- Conduct correlative analysis of exposure-response for measures of efficacy and changes in GC-modulated pathways, adrenocorticotrophic hormone (ACTH)/cortisol, or other PD markers.
- Assess the effect of pharmacogenomics polymorphisms of the cytochrome P450 pathway on PK and PD parameters (Dose-Determination Phase Segment 1 only).
- Explore the effects of exicorilant and enzalutamide on patient-reported outcomes (PRO) and quality of life (QoL).

4. Study Endpoints

The study has primary safety and secondary efficacy, safety and PK endpoints. Exploratory endpoints include efficacy, PD, PRO and QoL endpoints.

4.1. Primary Endpoint

This study includes a DLT endpoint to meet the primary objective of determining MTD and/or biologically active doses of exicorilant in combination with enzalutamide and to identify the RP2D.

DLTs will be recorded during the DLT-evaluation period (first dose of exicorilant through completion of Cycle 1 for Segment 1, or first dose of exicorilant through completion of Cycle 3 for Segment 2). The study protocol Section 5.5 defines a DLT as any of the following toxicities that the investigator considers possibly or probably related to study drug that occur during the DLT evaluation period:

- Hematologic DLT:
  - Grade 4 neutropenia for > 7 days.
  - Febrile Grade 3 or 4 neutropenia (absolute neutrophil count [ANC] <1000/mm^3 and a single temperature of >38.3°C [101°F] or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour).
  - Grade 3 thrombocytopenia with bleeding.
  - Grade 4 thrombocytopenia.
- Non-Hematologic DLT:
  - Grade 3 or greater toxicity according to National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) v4.03 that represents at least a 2-grade increase from baseline and is not attributable to disease or disease-related processes, with the following exceptions:
    - Grade 3 fever.
    - Grade 3 fatigue, nausea, vomiting, constipation, or diarrhea that resolves to Grade 2 or less within 48 hours after standard therapy.
    - Grade 3 changes in electrolytes not associated with signs or symptoms and that resolve within 3 days off therapy. An increase in gamma-glutamyl transferase (GGT) or alkaline phosphatase alone will not be considered a DLT.
    - Transient Grade 3 increase in creatinine or dehydration lasting ≤24 hours corrected with IV fluids if needed.
  - ALT >3x ULN with concomitant total bilirubin of >2x ULN.
- Grade 2 toxicity that represents at least a 2-grade increase from baseline, which requires dose modification or delay of >1 week.
- Failure to receive >25% of the doses during the DLT period due to toxicity.
- Dose delay due to AE of greater than 2 weeks.

Occurrences of DLTs will be collected by medical operation personnel and reviewed with investigators. These data will be used for the analysis of DLTs.

Per protocol Section 5.6, the MTD for exicorilant in combination with enzalutamide is the highest dose at which the DLT rate is <33% within the DLT-evaluation period. The DRC may determine a biologically active dose of exicorilant prior to reaching MTD based upon reliable evidence of GR antagonism and assessment of exposure-response for PD, tolerability, and efficacy. The RP2D of exicorilant in combination with enzalutamide will take into account overall tolerability, PD markers of target engagement, and PK. The RP2D will always be ≤ MTD.

4.2. Secondary Endpoints

4.2.1. Secondary Safety Endpoints

The safety and tolerability will be assessed by evaluating the following endpoints:

- Incidence of adverse events (AEs), serious AEs (SAEs), treatment-related AEs, AEs by severity, deaths
- Discontinuations of treatment and study withdrawal due to AEs
- Dose interruptions and reductions due to AEs
- Change from Baseline in clinical laboratory tests
- Change from Baseline in vital signs (including blood pressure, heart rate)
- Shift from Baseline in 12-Lead Electrocardiogram (ECG)
- Change from Baseline in Eastern Cooperative Oncology Group (ECOG) performance status

4.2.2. Secondary Efficacy Endpoints

Efficacy will be assessed by evaluating the following endpoints:

- ORR: proportion of patients with an objective tumor response (either partial response [PR] or complete response [CR]) per investigator using RECIST v.1.1 in patients with measurable disease, including best radiographic response for soft tissue.
- A reduction in PSA level from baseline by 50% or more.
- Time to SSE defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression.
- rPFS: time from first dose of study treatment (exicorilant and/or enzalutamide) to the date when the first site of disease is found to progress on computed tomography (CT), magnetic resonance imaging (MRI), or radionucleotide bone scan per the Prostate Cancer Working Group 3 (PCWG3) criteria, or death, whichever occurs first. Progression will be assessed by the investigator using RECIST v.1.1. The portion of patients who are progression-free at 4,6 and 12 months will also be summarized.
- DOR: time from the first occurrence of a documented objective tumor response (CR or PR) to the time of radiographic progression (per investigator using RECIST v.1.1) or death from any cause on study, whichever occurs first.
- Time to PSA progression, clinical progression (per investigator), and bone-disease progression.
- Overall survival: time from the first dose of exicorilant and/or enzalutamide to the date of death from any cause.

4.2.3. Secondary Pharmacokinetic Endpoints

PK will be assessed by evaluating the following:

- Standard PK parameters of exicorilant and enzalutamide will be estimated using non-compartmental methods to analyze the plasma concentration data for exicorilant and enzalutamide
- Determine the effect of food on the PK of exicorilant

4.3. Exploratory Endpoints

4.3.1. Exploratory Efficacy Endpoints

- Maximum reduction in PSA (% change) from baseline
- Best PSA response (i.e., the most post-baseline reduction in PSA (% change) among all the changes from every post-baseline PSA value to its prior largest PSA value)).

4.3.2. Patient-Reported Outcomes and Quality-of-Life Endpoints

PRO and Quality of life characteristics will be explored via the following endpoints:

- Median time to deterioration defined as the first occurrence of $\geq$ 10-point decrease from baseline on the overall Functional Assessment of Cancer Therapy-Prostate (FACT-P[1]) score.
- Change from baseline to each visit in the overall FACT-P score, as well as its subscales measuring physical and emotional well-being, prostate-cancer specific quality of life.
- Percentage of patients who filled out the survey and showed a 10-point improvement in FACT-P score.

4.3.3. Exploratory Pharmacodynamic Endpoints

- Change from baseline in serum cortisol and ACTH will be summarized by visit and arm.

5. Sample Size Calculation

The number of patients in the Dose-Determination Phase will depend on the number of cohorts assessed and the DLTs observed.

In Dose-Determination Phase Segment 1, an adequate number of DLT-evaluable patients will be enrolled to determine the RP2D for BID dosing. Expanded cohorts of 6 to 9 patients per dose level will be enrolled to better define the MTD/biologically active doses and for determination of the RP2D.

In Segment 2, approximately 20 patients will be enrolled (to achieve 16 DLT-evaluable patients) to determine the RP2D for QD dosing under fed conditions. Patients who discontinue treatment prior to completion of Cycle 3 and are not evaluable for DLTs may be replaced to include an adequate number of patients to assess the safety and tolerability of the regimen. If 2 to 4 patients are non-evaluable for DLTs, 4 additional patients will be enrolled. If 5 to 6 patients are non-evaluable for DLTs, 6 additional patients will be enrolled.

Approximately 40 patients will be enrolled in the Expansion Phase.

- Twenty patients in the Abi-Resistant Cohort will ensure at least 80% power for detecting a doubling of the background rate of 23.5% in the PSA responder, defined as ≥50% improvement in the PSA level from baseline. This calculation assumes a 1-sided 0.1 significance level exact test of a single proportion against a fixed alternative. Under these assumptions, an absolute response rate of 40%, which represents a 59% improvement over the background rate, will support further evaluation of the regimen in the clinical program.

- Twenty patients in the ARant-Resistant Cohort will ensure at least 80% power for detecting an absolute improvement of 18% in the PSA responder rate over a rate of 8%, based upon the assumption that a response rate of 8% or less indicates no benefit. This calculation assumes a 1-sided 0.1 significance level exact test of a single proportion against a fixed alternative. Under these assumptions, an absolute response rate of 20%, which represents an improvement of 12% over the background rate, will support further evaluation in the clinical program

6. Analysis Populations

6.1. Intent-To-Treat Analysis Population

Intent-to-Treat Population (ITT): All patients who received at least 1 dose of the combination (exicorilant + enzalutamide) study treatment. The ITT Population will be used for efficacy analyses.

6.2. Safety Analysis Population

Safety Population: All patients who received at least 1 dose of exicorilant. All safety analyses, except evaluation of DLTs, will be based on the Safety Population.

6.3. DLT Analysis Population

DLT-Evaluable Population: The DLT-Evaluable Population will include all patients in the Dose-Determination Phase cohorts who receive at least 1 dose of exicorilant and fulfill at least 1 of the following:

- Complete at least the following durations of study treatment:
    a. Segment 1: 28 days of continuous treatment with exicorilant
    b. Segment 2: 3 cycles (≥84 days) of exicorilant + enzalutamide
    c. Have received ≥75% of exicorilant and enzalutamide doses during the DLT-evaluation period
- Experience a DLT within the DLT-evaluation period.

Patients who have received <75% of the study regimen due to reasons other than toxicity or who withdraw from the study prior to completion of the DLT-evaluation period for reasons other than toxicity will be considered non-evaluable for DLTs.

6.4. Pharmacokinetics Analysis Population

The PK-Evaluable Population (PK population) will be a subset of the Safety population and will include all patients who receive active study treatment and have measurable plasma concentration of study treatment at any time point. Prematurely discontinued patients and patients with missing sample concentrations will be included in PK analyses provided their PK parameters can be adequately characterized based upon the remaining data. All PK analyses will be based on the PK population.

7. General Analytical Considerations

The statistical principles applied in the design and planned analyses of this study are consistent with International Council for Harmonisation (ICH) E9 guidelines (ICH 1998) and Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

All analyses will be completed using version 9.4 or later of the SAS Statistical Analysis System (SAS Institute, Inc, Cary, NC).

7.1. Data Sources

The study center staff will record completion and results of required study procedures in an electronic case report form (eCRF). Bioanalytical and laboratory data will be combined with the eCRF for analysis, after reconciled by [redacted]. CDISC SDTM domains will be prepared and used as the source data for the statistical summary and analysis.

7.2. Definitions

Study day: Study day will be calculated in reference to the date of the first dose of exicorilant. For assessments conducted on or after the date of the first dose of exicorilant, study day will be calculated as (assessment date-date of first dose of study drug + 1). For assessments conducted before the date of the first dose of exicorilant, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0.

Treatment-emergent period: The treatment-emergent period is defined as the period of time from the date and time of the first dose of exicorilant through 30 days after the last dose of

study drug (exicorilant or enzalutamide whichever is later). The treatment-emergent period will be used in the summaries of treatment-emergent adverse events (TEAEs).

Baseline and postbaseline value: Unless otherwise specified, a baseline value will be defined as the most recent value on or before the first dose of exicorilant including PRO, QoL and baseline characteristics. In addition, pretreatment Cycle 1 Day 1 values could serve as baseline. A postbaseline value is defined as an assessment obtained after the first dose of exicorilant.

Baseline and postbaseline value for safety analyses: Unless otherwise specified, a baseline value for safety analyses is defined as the last value on or before the date/time of first dose of exicorilant for laboratory tests, vital sign assessments, and ECG data. A postbaseline value for safety analyses is defined as a measurement taken after the date/time of first dose of exicorilant. If multiple toxicity grades are present for the same date, the worst toxicity grade will be used in the summaries of toxicity grade by laboratory tests. For triplicate measurements of ECG, worst results will be used in the summaries presented by visit. For all other safety parameters, if multiple measurements are present for the same date, latest available value will be considered for summaries.

Last dose date: Date of last dose of exicorilant or enzalutamide (whichever is last) from the end of treatment – exicorilant and enzalutamide eCRFs.

7.3. Reporting Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value.
- Percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).
- Listings will be sorted for presentation in order of patient identifier and date of procedure or event.
- Analysis and summary tables will have the analysis population sample size (ie, number of patients).
- Laboratory data will be reported using standard international (SI) units; as local laboratories are used for this study, conversion factors from conventional units will be listed in the clinical study report. For example: 1 inch = 2.54 cm.
- Time-to-event or duration of event endpoints will be based on the actual date the radiographic scan was obtained rather than the associated visit date.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator unless otherwise specified.

- For time-to-event right-censored data, the summary statistics and descriptions will include Kaplan-Meier plots and/or life tables.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and range (minimum and maximum).
- For categorical endpoints, the summary statistics will include frequency counts and percentages.
- Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, Clopper-Pearson method methods will be employed unless otherwise specified.
- Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v 20.1 or later. Adverse event severity will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v.5.0).
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical (ATC) therapeutic subgroup and preferred drug names.

PK Reporting Conventions:

PK parameters will be summarized using n (for available data), mean, standard deviation (SD), coefficient of variation percent (CV%), median, minimum, and maximum values, geometric mean, and geometric CV%.

Derived PK parameters will be rounded for reporting purposes in the by-patient listings. For calculation of descriptive statistics and statistical analysis, rounded values as presented in the data listings will be used. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g. C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g. t_{max}) will be reported to 3 decimal places.

Reporting of minimum, median, and maximum will follow the rounding convention of the individual PK variables. Means, any associated CI, and SD will be presented to one digit more precision than the source data. Coefficients of variation will always be reported to 1 decimal place.

Conventions for Dates:

Conventions for calculations with dates are as follows:

- Dates will be stored as numeric variables in the statistical analysis software (SAS) analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS).

- Dates recorded in comment fields will not be imputed or reported in any specific format.
- Intervals that are presented in weeks will be transformed from days to weeks by using the following conversion formula, and rounding to 1 decimal place: WEEKS = DAYS / 7
- Intervals that are presented in months will be transformed from days to months by using the following conversion formula, and rounding to 1 decimal place: MONTHS = DAYS / 30.4375

7.4. Handling of Missing Data

Missing data will not be imputed unless otherwise specified. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures.

For safety analyses, incomplete date of last dose of study drug and incomplete start date of a new antitumor treatment that are missing the day of the month, the 15th of the month will be used to impute the missing data. When imputing partial last dose dates, the last assessment date and death date will be taken into consideration. This imputation rule will be used to determine the treatment-emergent period.

Adverse Events

The imputation rule for the safety analyses will be used to address the issues with partial dates. The imputed dates will be used to determine the treatment-emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first of the month
- If only year is missing or start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If only year is missing or end date is completely missing, do not impute

Concomitant Medications

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If only year is missing or start date or end date of a medication is completely missing, do not impute.

Primary Cancer Diagnosis

If the diagnosis date of primary cancer is partially missing, the following rules will be applied to impute partial dates:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date.
- If both month and day are missing and year ≠ year of treatment start date, then set to December 31.
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date.
- If day is missing and month and year ≠ month and year of treatment start date, then set to the last day of the month

7.5. Visit Windows

Visit windows will be used to associate assessments with a scheduled visit for summarizing data by visit.

Visit windows are relative to Cycle 1 Day 1. In Cycle 1, the visit window for visits within Cycle 1 is a ±1-day window to the scheduled date, and the visit window is a ±3-day window to the scheduled date for visits in Cycle 2 or after. The post-treatment follow-up period starts after the final dose of study treatment (exicorilant or enzalutamide, whichever is latest). The

30-day–posttreatment follow-up visit will occur 30 days after the final dose of study treatment (exicorilant or enzalutamide, whichever is latest). Long-term phone follow-up for overall survival (ie, the date and cause of death, and post-treatment information) will continue every 4 months (±10 days) until the study endpoints are met or 2 years from the date that the last patient enrolls in the study (whichever is later).

All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window.

For efficacy assessments and AEs, data from both planned visits and unscheduled visits will be assessed and summarized. For all other by-visit safety assessments, unscheduled visits will be mapped into analysis visit windows as shown below (Table 2). If more than one assessment occurs within a given analysis visit window, (1) the planned visit will be always used in summaries for the given visit; (2) if all visits are unscheduled visits, the assessment closest to the target date will be used.

Table 2: Analysis Visit Windows for Safety Assessment

Visit Name	Start Day	Target Day	End Day
Cycle 1 Day 1	-28 or -7 or -1[a]	1	4
Cycle 1 Day 8	5	8	11
Cycle 1 Day 15	12	15	18
Cycle 1 Day 22	19	22	25
Cycle 2 Day 1	26	29	36
Cycle 2 Day 15	37	43	50
Cycle 3 Day 1	51	57	71
Cycle 4 Day 1	72	85	99
Cycle 5 Day 1	100	113	127
Cycle 6 Day 1	128	141	155
Cycle 7 Day 1	156	169	183
Cycle 8 Day 1	184	197	211
Cycle 9 Day 1	212	225	239
Cycle 10 Day 1	240	253	267
…	…	…	…
EOT		Study day of last dose of study drug	
EOT + 30 Days	Study day of last dose of study drug + 1	Study day of last dose of study drug + 30	Study day of last dose of study drug + 75
Post Treatment Follow-up 2	Study day of last dose of study drug + 76	Study day of last dose of study drug + 150	Study day of last dose of study drug + 210
…	…	…	…

[a] The Lead-In Period only applies to patients in Dose-Determination Phase Segment 1 and patients in the Expansion Phase Food-Effect Subcohort. Lead-in duration is 28 days in Dose-Determination Phase Segment 1, and 7 days for patients in the Expansion Phase Food-Effect Subcohort. The start day of cycle 1 day 1 is -28 for Dose-Determination Segment 1, -1 for Dose-Determination Segment 2, and -7 for Expansion Phase.

8. Statistical Methods

Analysis populations will be specified for each of the endpoints.

8.1. Patient Disposition

Patient populations will be summarized for all patients enrolled and will include the number and percentage of patients in each analysis population.

All patients who discontinue with the study will be included in a data listing. For each treatment group and overall, disposition summaries will present the number of enrolled patients, number of patients completing the study per protocol, and the number of patients terminating the study early by primary reason for discontinuation. Primary reason for discontinuation of treatment, including any of the following, will be summarized:

- Disease progression.
- AE(s).
- Investigator decision.
- Patient withdrawal of consent for treatment.
- Patient withdrawal of consent from study.
- Protocol non-compliance.
- Patient Died
- Unknown / lost to follow-up
- Other

Counts and percentages of patients who complete the study and those who discontinue for any of the following reasons will also be calculated:

- Death
- Lost to follow-up
- Study Terminated by Sponsor
- Withdrawal of consent
- Other

8.2. Protocol Deviations

Any noncompliance with the clinical trial protocol, good clinical practice (GCP), or manual of procedures (MOP) requirements, either on the part of the patient, the Investigator, or study site staff, will be considered a protocol deviation.

Protocol deviations will be categorized as important or other according to the protocol deviation specification document. Important protocol deviations that occur during the study will be summarized by deviation category by treatment regimen dose group/arm. A listing of all protocol deviations will be provided before database lock. This list will be maintained

cumulatively on the protocol deviation log and filed in the electronic Trial Master File (eTMF) at the end of the study.

8.3. Demographic Characteristics

The following patient characteristics collected at screening for the Safety population will be presented in data listings and summarized by treatment regimen and overall:

- Age at informed consent (continuous and categorical variable: <65, and ≥65)
- Sex
- Race
- Ethnicity
- Country/Territory of birth
- History of tobacco and alcohol use

8.4. Disease Characteristics and Previous Therapies

Prior cancer treatments include surgeries, systemic and radiation therapies will be summarized for ITT population.

Prior Anticancer Therapy for Prostate Cancer: All prior anticancer therapies received, and whether ongoing, will be listed by date of first dose. A summary table will be provided by treatment regimen dose group/arm and overall for number of patients reporting at least one prior anticancer therapy, prostate cancer disease status, best response achieved, and reason for discontinuation of therapy (toxicity, disease progression, or Other) and related information. Prior anticancer therapy for prostate cancer will also be summarized by following categories:

- Chemotherapy
- Immunotherapy
- Androgen deprivation therapy (ADT)
- Anti-androgens
- Secondary hormone therapy (excluding anti-androgens)
- Bone-targeted therapy
- Other

Prior Anticancer Therapy for Non-Prostate Cancer: A listing will display all entries for prior anticancer therapies received for non-prostate cancer. Summary statistics will be presented

for cancer type, administrative setting, best response, and reason for discontinuation for prior therapy.

Prior Radiotherapy: A listing will display all entries for prior radiotherapies received by date of first dose. For patients who received at least one prior radiotherapy, its indication, site, administrative setting, modality and total dose will be summarized by treatment regimen dose group/arm and overall.

8.5. Medical History

Non-Cancer Medical History:

As noted on the non-cancer medical history eCRF, relevant significant medical conditions will be presented in a listing and summary table. Verbatim terms will be coded using the MedDRA (version 20.1 or later) and ordered by system organ class and preferred term. At each level of summation (system organ class, preferred term), patients reporting more than one medical condition will be counted only once.

Cancer Medical History – Non-Prostate Cancer:

Patient history of non-prostate cancer, including type, date of original diagnosis, and stage at original diagnosis will be listed. A summary table will include counts and percent for type of cancer (in descending order of frequency) and stage at original diagnosis.

Prostate Cancer Medical History:

Details of prostate cancer medical history recorded on the eCRF, including total Gleason score, tumor histology at diagnosis, clinical tumor stage, clinical regional lymph nodes stage, and distant metastasis at initial prostate cancer pathological diagnosis will be listed and summarized.

Prior Prostate Cancer Procedures/Surgeries: A listing will be provided for all prior procedures and surgeries for prostate cancer.

Prior Cancer Panel/Molecular Profiling Results: Analysis may be described in the Biomarker SAP.

8.6. Prior and Concomitant Medications and Therapies

Any concomitant medication used by patients will be recorded on eCRF. Indication for use, whether taken for medical history or AE, start and end date, ongoing, dose, dose formulation, frequency, and route of administration will be noted. Medications are considered concomitant if exposure occurs during the treatment-emergent period. Medications missing both start and stop dates, or medications having a start date prior to the first dose of study product and missing the stop date, or medications having a stop date on or after the last dose of study product and missing start date will be counted as concomitant.

A patient reporting use of the same medication more than once will be counted once in the calculation of the number and percentage of patients who received that medication.

Verbatim terms from the eCRF will be mapped to Anatomical/Therapeutic Chemical (ATC) drug class (level 4) and generic drug names using the WHO Drug Dictionary (WHODD) Global B3 September 2019 coding dictionary.

For each treatment regimen dose group/arm, a listing will display all entries for medications received by a patient, ordered by "Start date". The listing will display the recorded term from the eCRF and, the ATC level 2 class (therapeutic subgroup) and the preferred/generic drug name.

A summary table will be organized to display the therapeutic subgroup (level 2) and preferred/generic drug name. It will include counts and percentages of patients who reported using at least one medication in each therapeutic subgroup by treatment regimen dose group/arm and overall.

A data listing will be provided for all concomitant procedures and/or surgeries.

Concomitant radiotherapy, blood transfusions, and subsequent anticancer therapies received will be listed and summarized by treatment regimen dose group/arm and overall.

8.7. Treatment Exposure and Compliance

All recorded information on oral dosing of exicorilant and enzalutamide, including dose level, frequency, and reason for dose interval changes will be presented in a data listing by date of administration. Note that daily dose was printed on the CRF, yet the data collected were dose level. To calculate the daily dose, we multiply the dose level with frequency. For the frequency of BID, the multiplier is 2. That is, daily dose equals to the dose level times 2. For the frequency of QD, the multiplier is 1. That is the dose level is the same as the daily dose.

A table by treatment regimen dose group/arm and overall will provide summary statistics on the following:

1) Number of Cycles of Treatment:
   The number of cycles for each study drug will be presented based on the last visit when the patient received treatment with non-zero and non-missing dose. The number of cycles for each study drug will be calculated as duration of exposure in weeks/4.
2) Duration of Exposure:
   The duration of exposure for each study drug will be presented in weeks and calculated as (the date of last non-zero and non-missing dose of study drug before drug discontinuation - the date of the first dose of study drug + 1)/7. Please note that if a patient had a lead-in period of a study medication, then the date of first dose for that study medication is the date of first dose in the lead-in period. If no lead in period, then start date of study drug is Cycle 1 Day 1.
3) Total Dose Received:

The total dose received for each study drug will be the sum of the actual dose administered during the duration of exposure. For subjects where their dose received is either zero or missing prior to drug discontinuation, a received dose of zero is included in the total dose received derivation.

4) Total dose expected:
The total dose expected is calculated for each study drug. The expected drug dosing schedule and the protocol-specified dose escalations, if any, is used in combination with the actual date and dose of study drug administration to calculate the total dose expected.
For Segment 1 of the Dose Determination Phase, the starting dose for both drugs in each cohort is its expected dose level.
For Segment 2 of the Dose Determination Phase, a protocol-specified dose escalation is expected for patients randomized to the Arm A group.
    - The expected dose of exicorilant for Segment 2 Arm A patient is 240 mg QD from Cycle 1 Day 1 to Cycle 1 Day 14, 280 mg QD from Cycle 1 Day 15 to Cycle 1 Day 28, and 320 mg QD thereafter.
    - The expected dose of exicorilant for Segment 2 Arm B patient is 240 mg QD.
    - The expected dose of enzalutamide for Segment 2 patient is patient's currently tolerated dose through the Screening Period and the initiation of exicorilant.
5) Relative dose intensity:
Relative dose intensity is calculated for each study drug as the total dose received divided by the total dose expected, multiplied by 100.

8.8. Dose Limiting Toxicity (DLT) Analyses

Prior to data unblinding, investigators will review AEs that occurred during the DLT-evaluation period and determine AEs that meet the DLT definition.

Dose-Determination Phase Segment 1

DLT analyses will be performed for DLT-evaluable population for patients in Dose-Determination Phase Segment 1, which include all patients who complete at least 1 cycle (4 weeks) of study treatment for segment 1 patients and have received ≥75% of doses for both exicorilant and enzalutamide during the DLT evaluation period, or who discontinue treatment due to toxicity.

Three patient cohorts were enrolled in Dose-Determination Phase Segment 1, which are
(1) Cohort 1: exicorilant 180mg BID/ enzalutamide 160 mg QD
(2) Cohort 2: exicorilant 140mg BID/ enzalutamide 160 mg QD
(3) Cohort 3: exicorilant 140mg BID/ enzalutamide 160 mg QD; No enzalutamide lead-in period

Number of patients with at least 1 DLT and number of DLTs will also be summarized by cohort, and overall.

Dose-Determination Phase Segment 2

DLT analyses will be performed for DLT-evaluable population for patients in Dose-Determination Phase Segment 2, which include all patients who complete at least 3 cycles (12 weeks) of study treatment for segment 2 patients and have received ≥75% of doses for both exicorilant and enzalutamide during the DLT evaluation period, (or equivalently, received ≥63 days of doses during the first 12 weeks for segment 2 patients), or who discontinue treatment due to toxicity.

Three study regimens will be evaluated for Segment 2 Arm A during the DLT-evaluation period, which are

(1) Regimen 1: 240 mg exicorilant + enzalutamide
(2) Regimen 2: 240-280 mg exicorilant + enzalutamide
(3) Regimen 3: 240-280-320 mg exicorilant + enzalutamide

DLT rate will be calculated for each study arm, study regimen and overall. The DLT rate for each study regimen is calculated as the ratio of the number of DLT-evaluable patients who experience at least one DLT during the treatment of any dose level of exicorilant from that study regimen to all DLT-evaluable patients.

One patient may experience more than one DLTs during the DLT evaluation period. Maximum Duration of DLTs will be calculated in weeks and is defined as the End Date of DLT – Start Date of DLT for the longest DLT time duration for each subject. Number of patients with at least 1 DLT, number of DLTs, and maximum duration of DLTs will be summarized by study regimen and overall.

DLT rate per patient-week will also be summarized by study arm, study regimen and overall, where the numerator is the number of patients with at least 1 DLT, and the denominator is the sum of patient's treatment duration (in weeks) during the DLT-evaluation period which is calculated as the days of the patients on treatment during the first 12 weeks divided by 7.

Number of patients with at least 1 DLT and number of DLTs will also be summarized by study arm, highest exicorilant dose level received, and overall.

8.9. Multiple Study Centers

Data analyses will be pooled and not controlled for center effect.

8.10. Sample Size Reassessment

Not Applicable.

8.11. Interim Analyses or Timing of Analyses

The DRC consisting of Investigators, the Medical Monitor, a Clinical Pharmacologist, and additional members as appropriate will review the safety, PK, and PD data following the

completion of each cohort during Dose-Determination Phase Segment 1, after all patients have completed 3 cycles of treatment in Dose-Determination Phase Segment 2, and at least every 6 months during the Expansion Phase.

An interim safety analysis will be conducted after a total of 20 patients complete 3 cycles of therapy in the Expansion Phase. If at any time during the Expansion Phase the DLT rate exceeds 33%, the dose will be declared non-feasible, and no additional patients will be enrolled to that dose. A lower dose level may be evaluated, per the recommendation of the DRC.

9. Efficacy Analyses

The recommendations of the PCWG3 will be used to determine disease response for this study. Tumor assessments include ^{99}mTc-methylene diphosphonate radionucleotide bone scintigraphy and CT of the chest, abdomen, and pelvis. Baseline tumor assessment will be performed within 28 days before the first dose of enzalutamide (for Dose-Determination Phase Segment 1) and/or the first dose of exicorilant (for Dose-Determination Phase Segment 2 and Expansion Phase). Post-baseline tumor assessments will be performed every 8 weeks after the first dose of enzalutamide and/or exicorilant for the first 24 weeks. Thereafter, tumor assessments will occur at intervals of 12 weeks until disease progression. Objective responses will be confirmed no less than 4 weeks after the criteria for response are first met (if possible, 4 – 6 weeks). PSA, alkaline phosphatase (ALP), and lactic dehydrogenase (LDH) will be assessed at the Baseline/Screening Visit and Day 1 of each cycle. The ITT population will be used to address the secondary and exploratory efficacy objectives of the study. Disease response and progression assessed according to RECIST v1.1 by the Investigator will provide the basis for efficacy endpoints.

At all scheduled visits, data recorded for target, non-target, and new lesions, and Investigator response assessment will be presented in by-patient listings. Summary tables and figures will be provided for endpoints as described in the following sections. Response rate endpoints will be summarized by providing the point and interval estimates. Time-to-event variables will be summarized using Kaplan-Meier estimates and plots.

9.1. Secondary Efficacy Endpoints

Objective Response Rate (ORR): Patient listings of tumor response outcomes (CR, PR, non-CR/non-progressive disease, stable disease, progressive disease, unevaluable, or not assessed) at study visits, as well as best overall response per RECIST v1.1, will be presented by treatment regimen dose group and overall for the ITT population. By-group summary tables will include distribution of response outcomes, best overall response derived over all visits, and point estimates with Clopper-Pearson[2] 95% CIs for ORR, defined as the proportion of patients with an objective tumor response (either PR or CR) in patients with measurable disease, including best radiographic response for soft tissue.

For supportive purposes, best overall response and point estimates with Clopper-Pearson 95% CIs for ORR will also be summarized using confirmed response.

PSA Levels: PSA levels recorded at each visit will be listed. Proportions of patients in the Safety population who experience a 50% or greater reduction in PSA levels at any visit since baseline will be reported with Clopper-Pearson 95% CIs by treatment group and overall. Mean reduction levels will be characterized via summary statistics. Median time from date of first dose of exicorilant to PSA progression (first occurrence of 50% or greater increase in PSA levels), along with 95% CIs will be estimated via Kaplan-Meier method, and also plotted graphically by treatment group. Patients who are alive and progression-free will be censored at the date of their-last PSA evaluation.

In dose escalation and expansion phases separately, best PSA response will be illustrated graphically via waterfall plots. For each patient, the maximum percent change in PSA levels since baseline will be depicted on the response axis, with vertical bars below the baseline representing decline in the blood-based marker.

Symptomatic Skeletal Event (SSE): SSE is defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression. SSEs include only symptomatic events of clear clinical significance. Kaplan-Meier estimates of median time from date of first dose of exicorilant to the first occurrence of SSE and associated 95% CIs, will be computed by treatment regimen dose group and overall for the Safety population. Patients who are event-free will be censored at the date of their end of study/treatment + 30 days visit. Kaplan-Meier graph of the probability of the event will also be constructed by treatment group.

Radiographic progression-free survival (rPFS): For the Response-Evaluable population, rPFS will be determined from the first dose of study treatment (exicorilant and/or enzalutamide) to the date when the first site of disease is found to progress on CT, MRI, or radionucleotide bone scan per PCWG3, or death, whichever occurs first. Progression will be assessed by the Investigator using RECIST v1.1.

> rPFS (months) = (earliest date of progression, death, or censoring – date of first study treatment + 1)/30.4375

Patients who do not experience disease progression or death (due to any cause) will be right-censored at the time of the last tumor assessment date. Censoring date will be based on the date patient was last known to be alive and progression-free (i.e., last assessment date) or data analysis cutoff date, whichever occurs first. Censoring rules are summarized in Table 3 below.

Table 3: Censoring Rules for the Primary Analysis of PFS

Censoring Categories	Date of Censoring
Patients who did not have baseline or postbaseline tumor assessments and did not die on or before the data cutoff date	Date of first study treatment

Patients who did not have disease progression as determined by the Investigator and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before the data cutoff date
Patients who did not have disease progression as determined by the Investigator on or before initiation of subsequent anticancer therapy for prostate cancer and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before initiation of subsequent anticancer therapy and on or before the data cutoff date
Patients who had 2 or more consecutive missed scheduled tumor assessments immediately prior to disease progression	Date of the last adequate tumor assessment without evidence of disease progression before the 2 missed tumor assessments and on or before the data cutoff date
Patients who did not have disease progression as determined by the Investigator and died more than 119 days from most recent tumor assessment.	Date of the last adequate tumor assessment on or before the data cutoff date

Note: If a patient meets the criteria for more than 1 censoring rule, PFS will be censored at the earliest censoring date.

Kaplan-Meier curves will be plotted by treatment regimen dose groups, and the estimate of median rPFS time (months) with 95% CI will be ascertained. For each cohort, progression-free rate at 4, 6, and 12 months will also be summarized.

Duration of response (DOR): Duration of response will be defined for patients in the Response-Evaluable population as the time from the first occurrence of a documented objective tumor response of CR or PR to the time of radiographic progression (per Investigator using RECIST v1.1) or death from any cause on study, whichever occurs first. Patients who have not experienced disease progression or death will be censored at the time of the last tumor assessment date. Date of censoring will be determined according to same rules as described for rPFS endpoint.

> DOR (months) = (earliest date of progression, death, or censoring – date of first documented objective response + 1)/30.4375

Kaplan-Meier graph will be plotted by treatment group and estimates of median duration with 95% CIs will be obtained for each dose cohort and overall. Patients who do not achieve a tumor response of CR or PR, will be excluded from this analysis.

Clinical progression*:* For the Response-Evaluable population, clinical disease progression, defined as time from first dose of study treatment (exicorilant and/or enzalutamide) to date of treatment discontinuation due to disease progression, will be estimated via the Kaplan-Meier

method. Patients who are alive and progression-free will be censored at their end of study visit. Median time to progression and associated 95% CIs will be summarized, overall and by treatment group. Kaplan-Meier graph of the probability of the event will also be plotted by treatment group.

Bone disease progression*:* For the Response-Evaluable population, bone disease progression, defined as time from first dose of study treatment (exicorilant and/or enzalutamide) to first confirmed appearance of at least 2 new bone metastatic lesions, will be estimated via the Kaplan-Meier method. Cases of equivocal progression will be confirmed by a repeat scan 8 weeks later. Patients who are alive and progression-free will be censored at their end of study visit. Median time to progression and associated 95% CIs will be summarized, overall and by treatment group. Kaplan-Meier graph of the probability of the event will also be plotted by treatment group.

Overall survival (OS): Overall survival will be calculated as the time from the first dose of study treatment (exicorilant and/or enzalutamide) to the date of death from any cause. Deaths that occur on or before the data cutoff date will be considered an event. If a patient has not died before the analysis cutoff date, OS will be censored at the date of last contact on or before the data cutoff date. The last contact date will be derived as follows:

Source Data Conditions	**Source Data Conditions**
Date of randomization	No condition
Last contact date/last date patient known to be alive from Long-Term Follow-Up eCRF	Use if patient status is reported to be alive Do not use if patient status is reported unknown
End of study	Not lost to follow up
Start/end dates of postbaseline antineoplastic therapy	Nonmissing medication/procedure term
Start/end dates from drug administration record	Nonmissing dose. Doses of 0 are allowed.
End of treatment date from the End of Treatment eCRF	No condition
Investigator overall tumor response assessment date	Evaluation is marked as done.
Laboratory/PK collection dates	Sample collection marked as done.
Vital signs date	At least 1 nonmissing parameter value
ECOG performance status date	Nonmissing ECOG performance status
Start/end dates of adverse events	Nonmissing verbatim term
Physical examination	Evaluation is marked as done.
ECG	Evaluation is marked as done.

The OS in months is defined as follows:

OS (months) = (earliest date of death or censoring – date of first study treatment + 1)/30.4375

Median, 25th and 75th percentiles of OS, in months, with 95% CIs will be summarized and plotted graphically by treatment arm and overall using the Kaplan-Meier method.

9.2. Exploratory Efficacy Endpoints

Change from baseline in PSA score: Summary statistics will be provided for PSA score at screening, baseline and at each of the post-baseline time points during the observation period. The changes of PSA score from baseline will be summarized by post-baseline visits. Patient data will be listed. Waterfall plots will be generated for maximum reduction in PSA (%) from baseline, and for best reduction in PSA (%) from any timepoint.

Patient Reported Outcomes (PRO) and Quality of Life (QoL) Assessments: PRO and QoL assessments will be listed and summarized using data from the Safety population.

The FACT-P questionnaire and additional questions to capture patient-reported pain will be used on study.

FACT-P: Patient responses to the 39 items of the instrument will be scored to obtain an overall and four subscale scores with lower scores indicating greater symptom burden. Possible ranges for the calculated scores would be:

- Overall (FACT-P): 0 – 156
- Physical Well-Being (PWB): 0 – 28
- Social/Family Well-Being (SWB): 0 – 28
- Emotional Well-Being (EWB): 0 – 24
- Functional Well-Being (FWB): 0 – 28
- Prostate Cancer Subscale (PCS): 0 – 48

Some items are reverse scored. Reversals will be performed as indicated by FACT-P Scoring Guidelines (Version 4) and individual items will be summed to obtain a score. If there are unanswered items, the total score will be multiplied by the number of items in the subscale and then divided by the number of items answered. This produces the subscale score. A higher score indicates better quality of life (QoL).

Health-related quality of life will be assessed in the Safety population and analysis subgroups (enzalutamide or abiraterone naïve, prior treatment with abiraterone, enzalutamide resistant, ARV7 positive and ARV7 negative, and GR positive and GR negative) using the FACT-P questionnaire at the time points shown in the SoA. Patients who discontinue exicorilant + enzalutamide due to reasons other than disease progression will continue to be assessed until unequivocal progressive disease is documented.

Patient listing for all subscales of FACT-P will be presented by visit and treatment group.

Specific endpoints to characterize the quality of life in patients will include:

- Median time to clinically meaningful deterioration defined as the first occurrence of ≥ 10-point decrease from baseline on FACT-P score with no subsequent observations with an increase of 10 or more points from baseline.
- Change from baseline to each visit in the overall FACT-P score, as well as its subscales, and pain-related score.
- Percentage of patients who filled out the survey and showed a >= 10-point improvement in FACT-P score, with no subsequent observations with a decrease of 10 or more points from baseline.

The distribution of time to deterioration will be summarized using the Kaplan-Meier method. The score and change from baseline in the FACT-P score and its subscales will be summarized by visit, by arm and overall. The baseline and post-baseline FACT-P score and its subscales will be analyzed using the paired t test for all patients in the ITT population.

Patient-Reported Pain: Additionally, at each study visit, patient-reported worst pain level within past 24 hours and its change from baseline will be summarized by arm and overall.

9.3. Subgroup Analyses

Analyses for preliminary efficacy and exploratory analyses for QoL will be done in all patients and in the following subgroups of patients, if a sufficient number of patients are evaluable in each subgroup:

- Enzalutamide and/or abiraterone naïve, had prior treatment with abiraterone, or are enzalutamide resistant.
- ARV7 positive or ARV7 negative circulating tumor cells at baseline
- GR+ or GR- negative circulating tumor cells at baseline
- GR+ or GR- biopsy at baseline/screening
- Line of therapy
- Systemic antagonism of cortisol activity

10. Safety Analyses

All safety analyses, except evaluation of DLTs, will use data from the Safety population. Relevant safety data collected through the course of the study on eCRF pages, including adverse events, deaths, clinical lab assessments, physical examination, vital signs, ECOG performance status, and 12-Lead electrocardiogram, will be presented in data listings and summary tables.

10.1. Adverse Events

Per protocol, adverse events will be collected from the time of signing the ICF until 30 days after the last dose of exicorilant or enzalutamide. Illnesses present before the patient signs the ICF will be considered pre-existing conditions and documented on the medical history eCRF.

Pre-existing conditions that worsen during the study will be entered on the AE eCRF. Adverse events that occur after the first dose of exicorilant through 30 days after administration of the final dose of study treatment will be considered treatment-emergent adverse events (TEAEs). Adverse events reported more than 30 days after the last dose of study treatment will be considered post-treatment AEs.

Incidence of TEAEs will be listed and summarized using the current version of Medical Dictionary for Regulatory Activities (MedDRA v20.1 or later) by system organ class and preferred term. A hierarchical listing will display the MedDRA system organ classes represented in the data, and within each system organ class, the listing will display each unique preferred term ordered alphabetically. At each level of summation of system organ class and preferred term, patients reporting more than one AE will only be counted once. Similarly, multiple incidences of the same AE for each patient will be reported only once at the maximum severity. If relationship to study drug is missing, the adverse event will be counted as related. Adverse event listings will show missing relationship as missing.

All AEs (whether TEAEs or not) will be listed in a listing by treatment group and individual patient, including dates of onset and resolution, whether ongoing, or serious, CTCAE toxicity grade, action taken and relationship to study drug. Serious TEAEs and TEAEs that lead to withdrawal from exicorilant or enzalutamide will be listed separately.

Summary tables will be provided for:

- Overall summary of TEAEs.
- TEAEs occurring 10% or higher in the Safety population by preferred term and CTCAE grade.
- All TEAEs.
- Grade 3 or greater TEAEs.
- TEAEs related to exicorilant.
- TEAEs related to enzalutamide.
- Grade 3 or greater TEAEs related to exicorilant.
- Grade 3 or greater TEAEs related to enzalutamide.
- Grade 3 or greater TEAEs related to exicorilant and enzalutamide.
- Serious TEAEs
- TEAEs leading to withdrawal of exicorilant.
- TEAEs leading to withdrawal of enzalutamide.
- TEAEs requiring dose interruption or reduction of exicorilant.
- TEAEs requiring dose interruption or reduction of enzalutamide.
- TEAEs requiring dose interruption or reduction of exicorilant and enzalutamide.

- AEs occurring only during enzalutamide lead-in period.

10.2. Deaths

All deaths, causes of death, and whether an autopsy report is available will be listed and summarized.

10.3. Clinical Laboratory Results

Clinical laboratory tests will be performed according to the SoA and samples analyzed at local laboratories. Results for hematology, serum chemistry, coagulation, urinalysis, PSA measurement, thyroid function, Hepatitis Serology and HIV, along with abnormal values where relevant, and normal ranges in reported and SI units will be presented in data listings. For list of laboratory tests, see Protocol Table 11.

Summaries of actual values and changes from baseline will be presented by treatment regimen dose group, by arm and overall, for each parameter and assessment time point. Change from Baseline will be calculated as the post-baseline minus the baseline measurement.

For parameters that can be graded using the NCI-CTCAE, shift tables that summarize counts and percentages of patients by severity grade at baseline and worst post-baseline result will also be constructed.

10.4. Vital Signs

At designated visits, vital signs will be recorded and will include weight, blood pressure, heart rate, respiration rate, and temperature. Listing of all vital signs data along with height, and derived BMI will be provided. Additionally, data will be summarized by treatment regimen dose group/arm, and overall, using descriptive statistics at baseline, each study evaluation, and change from baseline to each post-baseline evaluation. If either value is missing, the observation will not be included in the summary statistics.

10.5. 12-Lead Electrocardiogram

12-lead ECG (triplicate) is perform before dosing and approximately 2 hours post-dose (±10 minutes) on Cycle 1 Day 1 and Cycle 1 Day 15 (for all patients) and Cycle 3 Day 1 (for patients in Dose-Determination Phase Segment 1 only). At scheduled visits, 12-Lead ECGs will be obtained in triplicate (3 recordings made at intervals of at least 2 minutes apart) and presented in data listings. The Investigator or Sub-Investigator (physician) will be responsible for review and interpretation of the results and determining whether the ECG is normal, abnormal clinically significant, or abnormal not clinically significant. All recorded results will be included in a listing, and worst result of the triplicate readings at each visit will be summarized for each treatment arm as shift from Baseline.

10.6. ECOG Performance Status

Data listing for ECOG performance status assessed at Screening, at each study visit, and at the EOT and EOT + 30 days visit will be provided for each patient. Patient performance status will also be summarized by treatment regimen dose group/arm and overall for each numeric grade at baseline and change from Baseline.

11. Pharmacokinetic Analyses

The plasma PK of exicorilant, enzalutamide, and major metabolites, including M2 will be characterized in the PK-Evaluable Population using noncompartmental analysis, and analyte concentration versus time plot will be provided. The following PK parameters will be calculated, whenever possible, from plasma concentrations of exicorilant, enzalutamide, and M2, and combined exposure to both enzalutamide and M2:

- $AUC_{0\text{-}last}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time of last measurable concentration.
- $AUC_{0\text{-}24}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation.
- $AUC_{0\text{-}6h}$: AUC values from time 0 to 6 hours post-dose.
- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve from 0 to infinity, calculated as $AUC_{0\text{-}last} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant (whenever possible).
- C_{max}: Maximum observed plasma concentration.
- C_{last}: Minimum concentration from time 0 to time of last measurable concentration.
- $C_{min,ss}$: Minimum observed plasma concentration, at predose at steady-state.
- CL/F: Apparent oral clearance.
- T_{max}: Time of the maximum plasma concentration (obtained without interpolation).
- T_{last}: Time after dosing of the last quantifiable concentration.
- λ_z: Terminal elimination rate constant (whenever possible).

Missing dates or times may be imputed for PK samples if the missing values can be established with an acceptable level of accuracy based on other information during the visit in question. If PK sampling for a given patient is not performed according to protocol instructions, the corresponding concentration data may be excluded from the PK analyses.

PK parameters will be tabulated and summarized by treatment at baseline and scheduled time points using descriptive statistics. PK relationship to measures of efficacy or toxicity may also be explored. Additional PK analyses may be performed as deemed appropriate.

The effect of food on the PK of exicorilant will be evaluated in the first 10 patients enrolled in Cohort A of the Expansion phase. Mean time of maximum plasma concentration (T_{max}) will be compared in this Subcohort of patients under fed and fasting conditions, using a nonparametric test for dependent samples. The relationship of log transformed PK parameters C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ will be assessed with food using unadjusted and adjusted linear regression models that control for potential confounders. From these models, least-squares (LS) means, LS mean difference between fed and fasted conditions, and associated CIs will be obtained on the natural log scale. Transformed back from the logarithmic scale via exponentiation, ratios of geometric means under the two conditions and CIs will be estimated and presented. If the obtained 90% CIs for all three PK parameters fall outside the 0.80 – 1.25 range, a significant relationship between food effect and exicorilant will be concluded.

12. Pharmacodynamics and Pharmacogenomic Analyses

Biological samples (e.g., blood, plasma, serum, or tumor tissue) will be obtained from the Safety population for analysis during the study as well as for future analysis.

Summaries of actual values and changes from baseline in ACTH and serum cortisol will be presented by treatment regimen dose group, by arm and overall, for each parameter and assessment time point. Fold change in log2 scale from Baseline will be calculated as (log2(post-baseline measurement) - log2(baseline measurement))/log2(baseline measurement).

13. Change from Analyses Planned in Protocol

Definition of treatment emergent is updated from the protocol to be consistent with the definition of safety population (all patients who received at least one dose of exicorilant.) Per SAP Section 7.2 the treatment-emergent period is updated to be defined as the period of time from the date and time of the first dose of exicorilant (instead of study treatment) through 30 days after the last dose of study drug (exicorilant or enzalutamide whichever is later).

Definition of baseline is also updated from the protocol. Baseline is defined as the last measurement collected before the first dose of exicorilant (instead of exicorilant or on-study enzalutamide, whichever is earlier).

14. References

1. Osoba, D., Rodrigues, G., Myles, J., Zee, B., Pater, J. Interpreting the significance of changes in health-related quality-of-life score. J Clin Oncol. 1998; 16: 139-44.
2. Clopper, C.; Pearson, E. S. 1934. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 26 (4): 404–413.

3. FACT-P Scoring Guidelines (Version 4)
4. CORT125281-601 Protocol Amendment 5 Final 2020-02-21.pdf