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

NCT number: NCT03437941

Date: 21 February 2020

CLINICAL STUDY PROTOCOL CORT125281-601

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**
EudraCT Number	2017-003287-12
Investigational Product	CORT125281
Medical Monitor	[redacted]
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA (650) 327-3270
Version	Amendment 5
Date	21 February 2020

Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, the International Council for Harmonisation Good Clinical Practice guidelines, and with the ethical principles contained in the Declaration of Helsinki (1989), or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human study participants. Compliance with these standards provides assurance that the rights, safety, and well-being of study participants are protected.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

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APPROVAL STATEMENT

The undersigned has reviewed the format and content of the above protocol and approved for issuance.

SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study Number**
Corcept Therapeutics	CORT125281	CORT125281-601

Title of Study

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

Study Centers

Approximately 10 centers in the United States and United Kingdom

Phase of Development

Phase 1/2a

Duration of Treatment and Duration of Study

Patients will receive CORT125281 in combination with enzalutamide until reaching a protocol-defined event of disease progression, experiencing unmanageable toxicity, or until other treatment discontinuation criteria are met.

All patients will be followed for progression, information on subsequent anticancer therapies (start and end date and response) and survival.

Objectives

Primary Objective:

Determine the maximum tolerated dose (MTD) and/or biologically active doses of CORT125281 in combination with enzalutamide to identify the recommended dose (RD) for Phase 2 studies

Secondary Objectives:

- Evaluate the safety and tolerability of CORT125281 in combination with enzalutamide
- Characterize the preliminary efficacy of CORT125281 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, and overall survival
- Assess time to PSA progression and clinical progression, including the proportion of patients who are progression-free at 4, 6, and 12 months
- Determine the pharmacokinetic (PK) profile of CORT125281 and enzalutamide, when co-administered
- Determine the effect of food on the PK of CORT125281

Exploratory Objectives:

- Evaluate the effects of CORT125281 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 CORT125281 and enzalutamide by line of therapy and in specific sub-sets of disease, including:

- Glucocorticoid (GC) receptor (GR) positive versus GR negative, 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 analyses of exposure-response for measures of efficacy and changes in GC-modulated pathways, ACTH/cortisol, or other pharmacodynamic (PD) markers
- Assess the effect of the pharmacogenomic polymorphisms of the cytochrome P450 pathway on PK and PD parameters (Dose-Determination Phase Segment 1 only)
- Explore the effects of CORT125281 and enzalutamide on patient-reported outcomes (PRO) and quality of life (QoL)

Study Population

Patients with metastatic castration-resistant prostate cancer (mCRPC; prostate cancer that is resistant to medical or surgical treatments that lower testosterone) and patients with mCRPC with rising PSA, defined as a 25% increase over nadir and an absolute value >1 ng/mL, based on 2 measurements at least 1 week apart.

Methodology

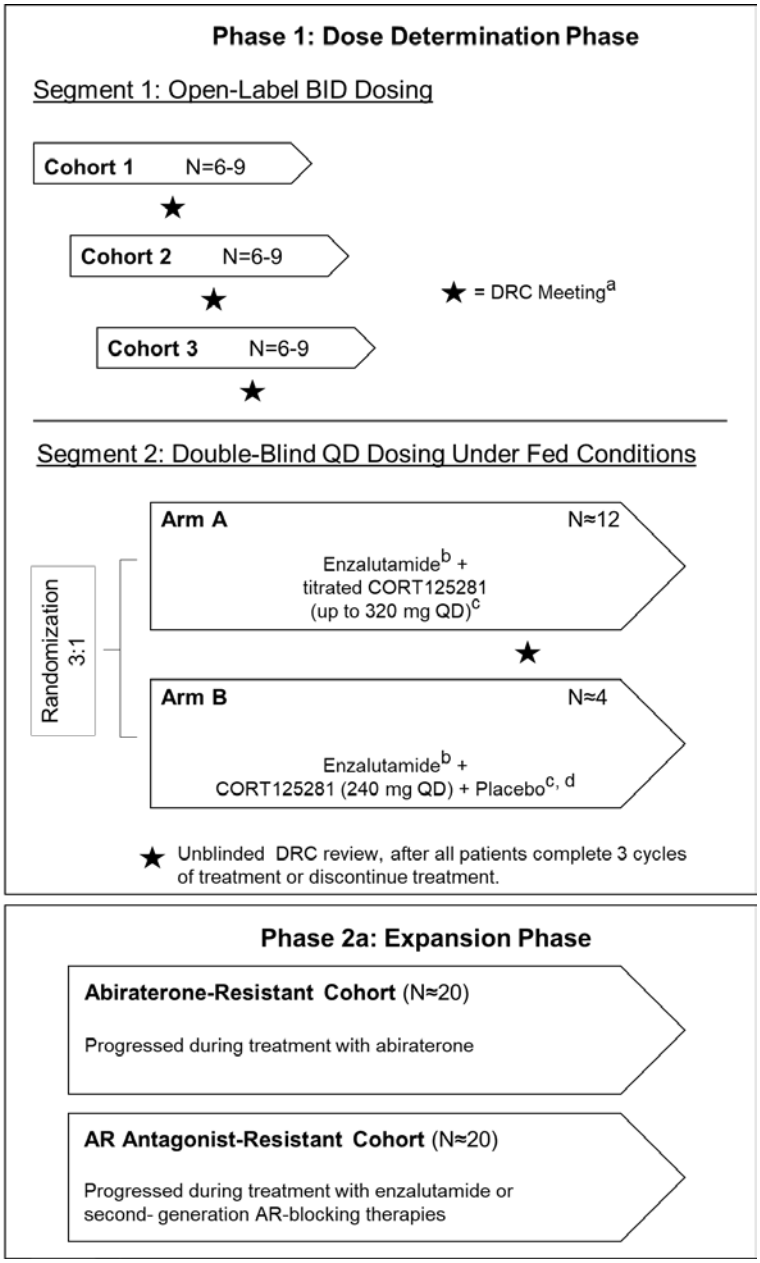
This is a Phase 1/2a, dose-determination and expansion study conducted in patients with mCRPC to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of CORT125281 in combination with enzalutamide; and to identify the RD.

The study (Figure S1) consists of the following phases:

- **Dose-Determination Phase (Phase 1):**
  - **Segment 1** (Open-Label, Twice Daily CORT125281): Patients enrolled in this segment will take CORT125281 twice daily (BID) in combination with enzalutamide once daily (QD). The starting dose in this segment of the study for CORT125281 is 180 mg BID, with subsequent dose cohorts to be determined based Data Review Committee (DRC) review of tolerability and PK data. Enzalutamide will be administered at a starting dose of 160 mg QD, with subsequent dosing to be determined based upon PK.
  - **Segment 2** (Double-Blind, Once Daily CORT125281 Under Fed Conditions): Patients in this segment will be randomized in a 3:1 ratio to Arm A (enzalutamide + titrated dose of CORT125281) and Arm B (enzalutamide + CORT125281 240 mg). All patients will take CORT125281 with food. Enzalutamide will be continued at the patient's currently tolerated dose through the Screening Period and the initiation of CORT125281. The DRC will review the frequency of dose-limiting toxicities (DLTs), the DLT rate (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 RD.
- **Expansion Phase** (**Phase 2a**, CORT125281 at the RD Under Fed Conditions): Once the RD has been determined in the Dose-Determination Phase, the following cohorts will be enrolled and treated with CORT125281 (with the RD regimen, under fed conditions) + enzalutamide. The DRC may elect to expand more than 1 dose level, if needed, to better define the RD:
  - Abiraterone (Abi)-Resistant Cohort: Patients who have progressed during treatment with abiraterone and no other AR-blocking therapies
  - Androgen-Receptor (AR) Antagonist (ARant)-Resistant Cohort: Patients who have progressed during treatment with enzalutamide or second-generation AR-blocking therapies

The overall study design is presented in Figure S1.

Figure S1 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 (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 CORT125281 to a maximum dose of 320 mg QD under fed conditions (Arm A) or with placebo (Arm B) to maintain a CORT125281 dose of 240 mg QD under fed conditions (Table S1).

[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 CORT125281 dose escalated per the recommended Phase 2 regimen.

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
  - Dose-Determination Phase Segment 2: No Lead-In Period
  - Expansion Phase:

    Food-Effect Subcohort only: A single dose of CORT125281 under fasting conditions on Cycle 1 Day -7, and a single dose of CORT125281 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 (CORT125281 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 CORT125281 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 CORT125281 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.

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

Segment 1 of the Dose-Determination Phase is designed to determine DLTs, the MTD/biologically active doses and the RD of CORT125281 + 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 RD. 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 CORT125281 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 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 CORT125281 will initially be in up to doubling steps until any DLT or Grade 2 toxicity attributed to CORT125281 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.

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 CORT125281 in combination with enzalutamide. All patients will receive CORT125281 at a starting dose of 240 mg QD under fed conditions. Approximately 20 patients will be enrolled to achieve 16 DLT-evaluable patients randomized in a 3:1 ratio to receive CORT125281 in combination with enzalutamide either with the starting dose of CORT125281 240 mg QD with dose titration to 320 mg QD (N=12; Arm A) or with the starting dose of CORT125281 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 CORT125281 should be taken with food.

All patients will start treatment with CORT125281 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 CORT125281. Beginning on Cycle 1 Day 16, the dose of investigational agent will be increased in 40-mg increments every 2 weeks, as tolerated, with either CORT125281 (Arm A; N=12) to a maximum dose of CORT125281 320 mg QD or with placebo (Arm B; N=4) (Table S1). 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)**: CORT125281 240 mg QD under fed conditions with upward dose titration in combination with enzalutamide. CORT125281 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 S1).
  - Cycle 1 Day 1: CORT125281 240 mg QD
  - Cycle 1 Day 16 (+14-day window): CORT125281 280 mg QD
  - Cycle 2 Day 2 to Cycle 2 Day 16 (+14-day window): CORT125281 320 mg QD
- **Arm B (N=4)**: CORT125281 240 mg QD under fed conditions, with an increase in the number of placebo capsules every 2 weeks (+14-day window) (Table S1).
  - Cycle 1 Day 1: CORT125281 240 mg QD
  - Cycle 1 Day 16 (+14-day window): CORT125281 240 mg QD
  - Cycle 2 Day 2 to Cycle 2 Day 16 (+14-day window): CORT125281 240 mg QD

Table S1 CORT125281 Upward Dose Titration for Dose-Determination Segment 2

Dose Level	Resulting CORT125281 Dosage (QD)		Open-Label Bottle (CORT125281)	Blind-Label Bottle (CORT125281 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 CORT125281 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 CORT125281 (Section 5.7).
[a] Note: The blind-label bottle contains blinded capsules (CORT125281 [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 CORT125281 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 RD. If the DLT rate for the regimen is ≥33%, alternative titration schemes may be considered as the regimen for the RD, 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 RD, patients assigned to Arm B who have not experienced dose reductions due to toxicity will have their CORT125281 dose escalated per the recommended Phase 2 regimen.

Phase 2a, Expansion Phase

Once the RD has been determined in the Dose-Determination Phase, the following cohorts will be enrolled and treated with CORT125281 + enzalutamide according to the RD regimen. The DRC may elect to expand more than 1 dose level, if needed, to better define the RD.

- **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 CORT125281 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 CORT125281 administered under fasting conditions.
    Day 1: Single oral dose of CORT125281 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 CORT125281 PK.

    Patients in the Abi-Resistant Cohort who do not participate in the food-effect study will not have a Lead-In Period.
- **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.

Criteria for Inclusion

Key Inclusion Criteria

- Able to understand the purpose and risks of the study; willing and able to adhere to scheduled visits, treatment plans, laboratory tests, and other study evaluations and procedures, and provide written informed consent.
- Males ≥18 years of age at the time of signing consent.
- Histologically confirmed adenocarcinoma of the prostate with metastatic disease.
- Dose-Determination Phase Segment 1 and Expansion Phase: Progressive disease as defined by PSA or imaging after most recent prior therapy. PSA ≥1 ng/mL, if a confirmed rise in PSA is the only indication of progression. Progression by PSA requires rising PSA over a previous reference value by at least 2 measurements obtained ≥1 week apart. PSA measurements can be collected during or after the most recent prior therapy.
- Dose-Determination Phase Segment 2: Currently receiving enzalutamide with a rising PSA as follows:
  - Rising PSA: 25% increase over nadir and an absolute value of >1 ng/mL by at least 2 measurements obtained ≥1 week apart. PSA measurements can be collected during or after the most recent prior therapy.
  - Patients must have received enzalutamide for a minimum of 12 weeks and be on stable doses of enzalutamide ≥80 mg QD for at least 4 weeks prior to Cycle 1 Day 1.

    Patients will continue enzalutamide without interruption during the Screening Period (no wash-out period).
    This will be the enzalutamide starting dose for combination with CORT125281 beginning on Cycle 1 Day 1.
  - M0 disease is allowed.
- Expansion Phase: Patients must have progressed while receiving an androgen-directed therapy, as follows:
  - Abi-Resistant Cohort: Patients must have progressed during treatment with abiraterone.

  - ARant-Resistant Cohort: Patients must have progressed during treatment with enzalutamide or second-generation AR-blocking therapies. Patients progressing on enzalutamide immediately prior to enrolling in this study must be on stable doses of enzalutamide. These patients will continue enzalutamide without interruption during the Screening Period (no wash-out period required).
- Prior surgical or chemical castration with serum testosterone <1.7 nmol/L (50 ng/dL). If the method of castration is use of a luteinizing hormone-releasing hormone (LHRH) analogue, there must be a plan to maintain effective LHRH analogue treatment for the duration of the trial.
- Consent to have all protocol-required PD biomarker samples. The pre-treatment and on-treatment paired tumor biopsies will be mandatory for a subset of patients.
- Consent to provide mandatory pharmacogenomic blood sample (Dose-Determination Phase Segment 1 Only).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Adequate baseline organ function within 14 days prior to the first dose of study treatment (enzalutamide and/or CORT125281, whichever is earlier).
- Patients receiving systemic corticosteroids greater than 2-weeks in duration within 3 months of study entry or with clinical evidence of adrenal insufficiency must have evidence of adequate adrenal function based upon morning plasma cortisol concentration or ACTH (cosyntropin) stimulation test.
- If a patient engages in sexual intercourse with a woman of childbearing potential, a condom with spermicide and another form of birth control must be used during and for 100 days after the final dose of study treatment (CORT125281 or enzalutamide, whichever is later). A condom is required during and for 100 days after completing treatment with enzalutamide if a patient is engaged in sexual activity with a pregnant woman. Patients must also agree to avoid sperm donation during the study and for at least 100 days after the final treatment administration.

Key Exclusion Criteria

- Received chemotherapy, non-palliative radiotherapy, immunotherapy, or any investigational cancer therapies within 21 days prior to the first dose of CORT125281, or treatment with such therapies is planned during protocol treatment. Concomitant anticancer therapy is not permitted during the enzalutamide Lead-In Period during Dose-Determination Phase Segment 1.
- More than 2 prior cytotoxic chemotherapy regimens for the treatment of mCRPC.
- The Dose-Determination and Expansion Phases will exclude patients for the following:
  - Dose-Determination Phase (Segment 1 only):
    - Progressed during treatment with enzalutamide prior to Cycle 1 Day -28 (only applies to patients receiving enzalutamide Lead-In) or
    - Received prior second-generation anti-androgen and require urgent disease response or stabilization
  - Expansion Phase, Abi-Resistant Cohort:
    - Received prior treatment with enzalutamide, or
    - Received prior second-generation anti-androgen and require urgent disease response or stabilization
  - Expansion Phase, ARant-Resistant Cohort: Require urgent disease response or stabilization
- Ongoing or anticipated therapy with hormone therapy (other than LHRH analogue), including any dose of megestrol acetate (Megace), finasteride (Proscar), dutasteride (Avodart) or received abiraterone within 28 days prior to the first dose of CORT125281.
- Contraindication or precaution for enzalutamide.
- Parenchymal brain metastases.

- Any clinically significant uncontrolled condition that may increase the risk to the study patient or that the Investigator considers places the patient at unacceptable risk.
- Received herbal products or alternative therapies that may decrease PSA levels or that may have hormonal anti-prostate cancer activity (eg, saw palmetto, PC-SPES, PC-HOPE, St. John's wort, selenium supplements, grape seed extract) within 21 days of study treatment initiation or plans to initiate treatment with these products/alternative therapies during the entire duration of the study.
- Received systemic GCs within 21 days prior to the first dose of CORT125281, or requirement for chronic or frequently used systemic or inhaled GCs for medical conditions (eg, rheumatoid arthritis, immunosuppression after organ transplantation). Short courses (≤5 days) for non-cancer-related reasons are allowed if clinically required (such as prophylaxis for computed tomography [CT]).
- Concurrent therapy with strong inhibitors or inducers of CYP3A4 or CYP2C8 or with sensitive substrates of CYP3A4, CYP2C9, or CYP2C19.

Study Drug, Dose, and Mode of Administration

Formulation: CORT125281 hard-shell capsules, 20 mg and 60 mg; CORT125281 softgel capsules, 40 mg

Dose:

- Dose-Determination Phase Segment 1: CORT125281, starting dose of 180 mg BID (hard-shell gelatin capsules), with subsequent dose levels to be determined based upon tolerability and PK
- Dose-Determination Phase Segment 2: CORT125281 starting dose of 240 mg QD (softgel capsules, with food), with titration of CORT125281 (Arm A) or placebo (Arm B). CORT125281 should be taken with the evening meal, unless otherwise specified.
- Expansion Phase: CORT125281 at the RD, as determined in the Dose-Determination Phase

Mode of Administration: Oral

Reference Product, Dose, and Mode of Administration (Dose-Determination Phase Segment 2 Only)

Formulation: Placebo softgel capsules to match the appearance of the CORT125281 softgel (40 mg) capsules

Dose: No active (CORT125281) ingredient (0 mg)

Mode of Administration: Oral

Enzalutamide Dose and Mode of Administration

Formulation: Enzalutamide capsules, 40 mg

Dose:

- Dose-Determination Phase Segment 1: Enzalutamide at the starting dose of 160 mg QD, with subsequent dosing to be determined based upon PK
- Dose-Determination Phase Segment 2: Enzalutamide at the patient's currently tolerated dose at baseline. Enzalutamide should be taken once a day (the time of day is per the Investigator's discretion, except where noted for days with PK/PD sample collections).
- Expansion Phase: Enzalutamide 160 mg QD if not currently receiving enzalutamide or at the patient's currently tolerated dose at baseline if ongoing from the immediately preceding line of therapy

Mode of Administration: Oral

Criteria for Evaluation

The SoAs are provided in Appendix A.

Efficacy Assessments

Tumor assessments will include ^{99}mTc-methylene diphosphonate radionucleotide bone scintigraphy and CT of the chest, abdomen, and pelvis within 28 days before the first dose of enzalutamide (for Dose-Determination Phase Segment 1) and/or CORT125281 (for Dose-Determination Phase Segment 2 and the Expansion Phase) and at intervals of 8 weeks after the first dose of study treatment for the first 24 weeks. Thereafter, tumor assessments will occur at intervals of 12 weeks until disease progression. Blood-based markers (PSA, alkaline phosphatase, and lactic dehydrogenase) will be assessed within 28 days prior to the first dose of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier) and on the first day of each cycle. The recommendations of the Prostate Cancer Working Group (PCWG3), incorporating modified Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), will be used to determine response (Eisenhauer et al. 2009; Scher et al. 2016). All patients will continue to be followed until the study endpoints are met (radiographic disease progression, SSE, and overall survival). Follow-up for overall survival (ie, the date and cause of death, and post-treatment information) will continue every 4 months until 2 years from the date that the last patient enrolls in the study or until all patients have completed follow-up for radiographic disease progression (whichever is later).

Safety Assessments

The safety of each treatment group will be assessed by evaluating exposure to the study treatments (CORT125281 and enzalutamide), AEs, serious adverse events (SAEs), all deaths, changes in laboratory determinations, and vital sign parameters. The Safety Population will include all patients who received at least 1 dose of CORT125281.

Pharmacokinetic Assessment:

The plasma concentration data for CORT125281, CORT125324 (metabolite of CORT125281), enzalutamide, N-desmethyl enzalutamide (M2, the active metabolite of enzalutamide), and enzalutamide carboxylic acid (inactive metabolite of enzalutamide) will be analyzed using non-compartmental methods to obtain estimates of standard PK parameters. The effect of food on the PK of CORT125281 will be analyzed.

Pharmacogenomic Assessment

Whole blood will be collected at baseline during Dose-Determination Phase Segment 1, for assessment of genes involved in the metabolism, safety and efficacy of CORT125281 and enzalutamide.

Pharmacodynamic Assessments

Samples will be collected for the following assessments:

- Tumor expression of GR via IHC
- Assay of messenger RNA (mRNA) expression of GC-modulated pathways, in whole blood and tumor
- CTCs: enumeration, GR expression, ARV7, and exploratory biomarkers
- Plasma ACTH, serum cortisol, 24-hour UFC (and creatinine), and spot urine test for cortisol (and creatinine) to assess modulation of the HPA axis
- Dehydroepiandrosterone-sulfate (DHEA-S), androstenedione, testosterone (free and total) and estradiol levels
- Whole blood for exploratory biomarkers, such as circulating tumor deoxyribonucleic acid (DNA)
- Neutrophil-to-lymphocyte ratio and relative abundance of other cells in the blood (from the complete blood count)

Patient-Reported Outcomes and Quality-of-Life Assessments

Health-related PRO and QoL will be assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, with additional questions to capture patient-reported pain.

Statistical Methods

Sample Size

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 RD 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 RD. In Segment 2, approximately 20 patients will be enrolled (to achieve 16 DLT-evaluable patients) to determine the RD 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.

Statistical Analyses

Analyses of safety and anticancer activity for this dose-determination and expansion Phase 1/2a study will focus on estimation of treatment effects via descriptive statistics and confidence intervals. Kaplan-Meier methods will be used for time-to-event endpoints. In Dose-Determination Phase Segment 1 and in the Expansion Phase, all analyses will be presented by treatment dose regimen and overall. In Dose-Determination Phase Segment 2, all analyses will be presented by treatment arm and overall.

To meet the study primary objective of determining the MTD/ biologically active doses of CORT125281 in combination with enzalutamide, the number, percent and duration of DLTs according to the NCI-CTCAE, version 4.03, will be summarized.

To meet the study secondary objective to evaluate the safety and tolerability of CORT125281 in combination with enzalutamide the following analyses will be performed.

The incidence of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the final dose of study treatment, will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term by treatment dose regimen and overall. Treatment-emergent AEs will be further summarized by severity and relationship to study treatment.

The following adverse events will be summarized separately: adverse events leading to withdrawal of study treatment (CORT125281 or enzalutamide), dose reduction or interruption, Grade 3 or greater AEs, and SAEs.

All deaths and causes of deaths will be summarized and listed.

To meet the secondary objective of characterizing anticancer activity, the following endpoints will be summarized:

- ORR, defined as the proportion of patients with an objective tumor response (either partial response [PR] or complete response [CR] per Investigator using RECIST v1.1) in patients with measurable disease, including best radiographic response for soft tissue
- A reduction in PSA level by 50% or more
- Distribution of the best PSA response
- Time to SSE defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression
- rPFS, defined as the time from the first dose of study treatment (CORT125281 and/or enzalutamide) to the date when the first site of disease is found to progress on CT, magnetic resonance imaging (MRI), or radionucleotide bone scan per PCWG3, or death, whichever occurs first. Progression will be assessed by the Investigator using RECIST v1.1. Proportion of patients who are progression-free at 4, 6, and 12 months will also be summarized.
- Duration of Response (DOR), defined as the time from the first occurrence of a documented objective tumor response to the time of radiographic progression (per Investigator using RECIST v1.1) or death from any cause on study, whichever occurs first
- Time to PSA progression, clinical progression (per Investigator), and bone disease progression
- Overall survival, defined as the time from the first dose of study treatment (CORT125281 and/or enzalutamide) to the date of death from any cause

For the analyses of rPFS and DOR, data for the patients who have not experienced disease progression or death will be censored at the time of the last tumor assessment date.

Data for the analysis of overall survival will be censored at the time of the end of follow-up period.

Analyses for preliminary efficacy will also be assessed in the following subgroups of patients, if a sufficient number of patients are evaluable in each subgroup:

- Enzalutamide and/or abiraterone naïve
- Prior treatment with abiraterone
- Enzalutamide resistant
- ARV7 positive and ARV7 negative (defined by positive on CTC and/or liquid biopsy, or most current definition at the completion of the study)
- GR positive and GR negative (defined by IHC and/or CTCs)

PK parameters of enzalutamide, CORT125281, and their metabolites will be calculated and analyte concentration versus time plots will be provided. The PK of CORT125281 will be analyzed by analysis of variance (ANOVA) adjusted for food effect and other potential factors that may influence the outcome. The size of the food effect will be estimated using 90% confidence intervals based on the model. PD parameters will be listed and summarized using descriptive statistics.

Exploratory analyses will characterize PRO and QoL using the following endpoints:

- Median time to deterioration defined as ≥10-point decrease from baseline on the overall FACT-P score
- Change from baseline in the overall FACT-P scores, as well as its subscales measuring physical and emotional well-being, prostate cancer-specific QoL, and pain-related score

- Percentage of patients who filled out the survey and showed improvement in FACT-P, and its subscales

Additional exploratory analyses to evaluate the effects of CORT125281 and enzalutamide on pain and time to worsening of pain will be prespecified in the Statistical Analysis Plan.

Interim Safety 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.

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LIST OF ABBREVIATIONS AND DEFINITIONS

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
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AR	androgen receptor
ARant	androgen-receptor antagonist
ARV7	androgen-receptor splice variant 7 messenger RNA
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the curve from 0 to 24 hours
AUC_{0-inf}	area under the curve from 0 to infinity
BID	twice daily
BRCA1 and BRCA2	BReast CAncer Genes 1 and 2
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{min}	minimum concentration
CRPC	castration-resistant prostate cancer
CR	complete response
CT	computed tomography
CTC	circulating tumor cell

Abbreviation	Definition
CYP	cytochrome P450
DHEA-S	dehydroepiandrosterone-sulfate
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
FDA	Food and Drug Administration
FT3	free triiodothyronine
FT4	free thyroxine
GC	glucocorticoid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GR	glucocorticoid receptor
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
IB	Investigator's Brochure
IC_{50}	concentration required to reduce response by half
ICH	International Council for Harmonisation
ICF	informed consent form

Abbreviation	Definition
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
Ki	inhibition constant
LDH	lactic dehydrogenase
LHRH	luteinizing hormone-releasing hormone
M2	N-desmethyl enzalutamide, the active metabolite of enzalutamide
MAD	multiple-ascending dose
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect-level
ORR	objective response rate
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time

Abbreviation	Definition
QC	quality check
QD	once daily
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SOC	system organ class
SOD	sum of diameters
SOP	Standard Operating Procedure
SSE	symptomatic skeletal event
SUSAR	Suspected Unexpected Adverse Reactions
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
TSH	thyroid-stimulating hormone
TT3	total triiodothyronine
UFC	urinary free cortisol
ULN	upper limit of normal
US	United States
USPI	United States Package Insert

1 INTRODUCTION

1.1 Castration-Resistant Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men and is a major contributor to cancer deaths in developed countries. As prostate cancer growth is driven by androgens, androgen-deprivation therapy with gonadotropin-releasing hormone analogues is the mainstay of therapy for patients with locally advanced or metastatic prostate cancer.

While the testes normally contribute the majority (90% to 95%) of androgen production, the remaining 5% to 10% is produced by the adrenal glands resulting in intratumoral androgen levels similar to those in the non-castrated prostate. Thus, there is still a role for further targeting androgen levels and androgen receptor (AR) signaling. Recently approved hormone-based therapies include abiraterone, which inhibits androgen synthesis, and enzalutamide, an AR antagonist. Both enzalutamide and abiraterone have demonstrated a survival advantage in both post-docetaxel as well as chemotherapy-naïve patients. Additional options for the treatment of castration-resistant prostate cancer (CRPC) include immunotherapy with Sipuleucel-T in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC (mCRPC), or chemotherapy with docetaxel or cabazitaxel, and treatment of bone metastases with the alpha emitter, radium-223 (in those without visceral disease). Choice and sequencing of therapy is based primarily on clinical considerations, such as presence or absence of visceral disease, symptoms, patient preferences, prior treatment, and potential side effects.

1.2 Therapeutic Hypothesis

In patients with CRPC treated with anti-androgen therapy, the glucocorticoid (GC) receptor (GR) can become the dominant growth factor and provides a mechanism of resistance to drugs such as enzalutamide. The therapeutic hypothesis is that treatment with a GR antagonist in combination with enzalutamide will overcome a mechanism of resistance to androgen-targeted therapies. The combination will thereby provide clinical benefit to patients with mCRPC, compared with enzalutamide alone, as well as to patients who have developed enzalutamide resistance. Cross-talk between steroid nuclear receptor signaling pathways and transcriptional activity has been described for the GR and AR, with increased expression of anti-apoptotic genes such as serum/GC-regulated kinase 1 (Isikbay et al. 2014). In nonclinical models of prostate cancer with intact AR signaling, GR activation has been reported to inhibit cell growth (Smith et al. 1985). In contrast, in prostate cancer cell lines that lack AR signaling (androgen-independent) but express GR, GR activation promotes cell proliferation, with the GR antagonist, mifepristone (Korlym®), blocking this effect (Gabaglia et al. 2010, Yan et al. 2008). GR antagonism has been reported to restore sensitivity to enzalutamide (Arora et al. 2013), and GR depletion has been reported to delay CRPC formation in nonclinical models (Isikbay et al. 2014). In nonclinical models, the combination of a GR antagonist and castration offers benefit compared to castration alone (see Section 1.3, Kach et al. 2017). Retrospective analyses have demonstrated increased GR expression in primary tumor samples from patients treated with androgen-deprivation therapy (Szmulewitz et al. 2012, Yemelyanov et al. 2012) and in bone metastases from patients receiving enzalutamide (Arora et al. 2013), supporting the clinical relevance of this mechanism. A post-hoc analysis of the Phase 3 AFFIRM clinical trial found that men with mCRPC receiving

corticosteroids had significantly worse survival than those who did not (Scher et al. 2012a, Scher et al. 2012b).

1.3 CORT125281: A Glucocorticoid Receptor Antagonist

CORT125281 (International nonproprietary name: exicorilant) is a selective GR antagonist that is being developed for the treatment of mCRPC. The goals of the study are: (1) to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of oral doses of CORT125281 in combination with enzalutamide in patients with mCRPC and (2) to select the recommended regimen for further development.

Detailed information about CORT125281 is provided in the current Investigator's Brochure (IB). This section summarizes the key data that are relevant to this study.

1.3.1 Nonclinical Data

1.3.1.1 Pharmacology Related to Mode of Action

This section summarizes in vitro and in vivo data relating to the pharmacology of CORT125281 as a GR receptor antagonist. In most models, mifepristone was used as an active comparator. Mifepristone is an antagonist of the progesterone receptor and AR as well as the GR. It was initially developed as an abortion agent based on its progesterone receptor antagonism but, based on its GR antagonism, is now approved in the United States (US) for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery (Korlym 2019). CORT125281 is a novel agent with similar GR antagonism without effects at the progesterone receptor or AR.

1.3.1.1.1 In Vitro Results

CORT125281 is a high-affinity, competitive, reversible, full antagonist (no agonist activity) of the human GR, with inhibition constants (Ki) <1 nM in a human GR binding assay and <15 nM in a human functional assay. It was approximately 2- to 4-fold less potent than mifepristone, in these assays. In common with mifepristone, CORT125281 is a partial agonist in the rat. In vitro, it is a full antagonist at the mini pig GR.

1.3.1.1.2 [redacted]

[redacted]

[redacted]

1.3.1.1.3 Pharmacologically Active Dose Range

In common with other GR antagonists, CORT125281 is effective in the rat cortisone-induced model of insulin resistance. In this model, insulin resistance is induced by repeated administration of a GR agonist. Data from this model can be used to derive a pharmacologically active dose range. The ability of CORT125281 to inhibit the effects of the agonist was assessed at several doses. The minimally effective dose was 3 mg/kg twice a day, and the highest dose tested was 30 mg/kg twice a day.

1.3.1.2 [redacted]

[redacted]

[redacted]

1.3.1.3 Pharmacokinetics

1.3.1.3.1 Single-Dose Pharmacokinetics

In the rat, following intravenous (IV) administration of CORT125281, 1 mg/kg, plasma clearance was moderate (0.635 L/h/kg), volume of distribution was high (2.1 L/kg) and half-life ($t_{1/2}$) was short (2.83 hours). Following oral administration of a 5 mg/kg dose, $t_{1/2}$ was moderate (approximately 5.5 hours) and bioavailability excellent (approximately 100%). In subsequent studies using oral administration, PK parameters depended upon formulation.

In the mini pig, following intravenous administration of CORT125281, 1 mg/kg, plasma clearance was moderate (0.86 L/h/kg), and both volume of distribution (21.941 L/kg) and $t_{½}$ (35.17 hours) very high. Oral bioavailability was excellent (84%), although the time to reach C_{max} (T_{max}) was late (8 hours).

[redacted] A single-dose study was conducted in the mini pig to determine the effect of the formulation on oral bioavailability. In this study, the anticipated clinical formulation provided adequate exposure, although both C_{max} and AUC were lower than the values observed in the initial study using the toxicology formulation.

1.3.1.3.2 [redacted]

[redacted]

1.3.1.3.3 Absorption, Distribution, Metabolism and Elimination

CORT125281 is highly protein bound in rat (99.9%), mini pig (99.7%), and human (99.9%).

The metabolite profile of CORT125281, assessed by incubation with cryopreserved hepatocytes, was qualitatively similar in rat, mini pig, and human.

In vitro studies with human cytochrome P450 (CYP) isoforms indicated that CORT125281 was metabolized primarily by CYP3A4 (49.3%) but with minor contributions from a range of other CYPs.

In vitro, CORT125281 is a potent inhibitor of CYP3A4 (concentration required to reduce response by half [IC_{50}] 0.1 µM) and CYP2C8 (IC_{50} 0.59 µM); partial inhibition of CYP2C9 was also noted (IC_{50} 0.8 µM). There was some evidence that CORT125281 may induce CYP1A2 and CYP3A4.

1.3.2 Clinical Data

At the time of initiation of this study, no studies of CORT125281 had been completed in humans. Safety clinical data are available for mifepristone, a marketed antagonist of GR and other steroid receptors, and CORT125134, another investigational GR antagonist that is in clinical development by Corcept (hereafter referred to as the "Sponsor").

Mifepristone (Korlym 2019) is generally well tolerated, with the most frequently reported adverse reactions (reported in ≥20% of patients, regardless of relationship to Korlym) were nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy.

CORT125134, which is structurally related to CORT125281, has been evaluated in Phase 1 clinical studies in healthy volunteers, including a single-ascending dose (SAD)/ multiple-ascending dose (MAD) trial (Study CORT125134-120) and is currently under evaluation in separate patient population trials: oncology (Phase 1/2 [NCT02762981] and Phase 2 [NCT03776812]) and Cushing syndrome (Phase 3 [NCT03697109] and extension study [NCT03604198]). In Study CORT125134-120, single-ascending doses up to 500 mg were well tolerated. Daily dosing for 14 days was well tolerated for dose up to 250 mg, but 500 mg administered daily was not tolerated and the study was stopped prematurely at that dose level. Musculoskeletal and connective tissue disorders (back pain and musculoskeletal pain) were the most frequently reported dose-limiting symptoms. It is not known whether these effects are caused by GR antagonism or are an off-target effect.

1.3.2.1 Clinical Update

As of 18 February 2020, two Phase 1 studies (CORT125281-600 and CORT125281-602) have completed with CORT125281 in healthy subjects, and data are available for 12 patients who have received CORT125281 in combination with enzalutamide in CORT125281-601. This information is briefly summarized below.

Please refer to the most recent CORT125281 IB for further details related to clinical experience with CORT125281 and current safety information.

CORT125281-600

This was the first-in-human study of CORT125281. The study consisted of separate SAD and MAD phases. The first dose level in the MAD part of the study was 120 mg daily. PK parameters at this dose level supported the rationale for administering CORT125281 twice daily (BID), which was employed for the next 2 cohorts (180 mg and 240 mg BID). However, with repeated dosing at these dose levels, a slower terminal elimination phase became apparent and, in the final cohort, an intermediate once daily (QD) dose (360 mg) was evaluated to explore whether this regimen could be used in future studies.

Within-subject comparisons of CORT125281 PK after administration of a single dose of 360 mg CORT125281 under fed and fasted conditions were possible in 3 subjects. The median T_{max} of CORT125281 was 4.08 hours in the fed state and 2.00 hours in the fasted state. The geometric mean C_{max} of CORT125281 was approximately 47% lower under fed versus fasted conditions, while the AUC of CORT125281 was similar when dosed fed or fasted. PK parameters were calculated for multiple doses of CORT125281. Following QD or BID administration of CORT125281 for 14 days, the plasma concentrations of CORT125281 increased at each dose level with repeated dosing, with an approximately 2- to 4-fold increase in exposure. The greatest accumulation in CORT125281 concentrations upon multiple dosing was observed following dosing with CORT125281 240 mg BID. Additionally, CORT125281 plasma concentrations increased in a greater-than-dose-proportional manner between CORT125281 120 mg QD and 360 mg QD, and between CORT125281 180 mg BID and 240 mg BID.

In accordance with the study design, subjects in the MAD part of the study took part in 3 study epochs: 15 mg pioglitazone alone; randomized study treatment alone; and randomized study treatment with a single concomitant dose of 15 mg pioglitazone. For the purpose of assessing the safety of CORT125281, the focus of this section is on treatment-emergent adverse events (TEAEs) occurring during the period with randomized study treatment alone.

Treatment-related gastrointestinal disorders and musculoskeletal and connective tissue disorders were reported only by subjects treated with CORT125281 and with a generally increasing incidence with dose. Within the system organ class (SOC) gastrointestinal disorders, the preferred terms nausea, abdominal discomfort, and diarrhea were reported by ≥10% of subjects treated with CORT125281, with single reports of abdominal pain, constipation, dyspepsia, gastroesophageal reflux disease, mouth ulceration and vomiting. Within the SOC musculoskeletal and connective tissue disorders, back pain and neck pain were reported, with a single report of joint stiffness. Ear and labyrinth disorders (ear pain, tinnitus, ear discomfort, and ear congestion) and nervous system disorders (headache, somnolence, and dizziness) were reported by generally similar proportions of subjects across all treatment groups including placebo.

In total, 2 TEAEs were graded severe in intensity: abdominal pain in a subject treated with CORT125281, 240 mg BID and back pain in a subject treated with CORT125281, 360 mg QD after concomitant pioglitazone.

CORT125281-601

In the current study, a total of 14 patients with mCRPC have been enrolled to 3 sequential dose-finding cohorts to evaluate CORT125281 BID under fasting conditions in combination with

enzalutamide 160 mg QD. Twelve patients have received CORT125281 in combination with enzalutamide, and 2 patients discontinued the study during the enzalutamide lead-in and did not receive CORT125281. In Cohort 1, two patients received CORT125281 180 mg BID with enzalutamide. Both patients experienced dose-limiting toxicities (DLTs), including Grade 3 fatigue (n=1), and the concurrent SAEs of Grade 3 fatigue and Grade 3 musculoskeletal pain (n=1); thus CORT125281 180 mg BID was deemed intolerable. A lower dose (CORT125281 140 mg BID) was evaluated in Cohort 2. In Cohort 2, 1 of 3 patients experienced a DLT (SAE of Grade 3 acute pancreatitis). After the third patient enrolled to Cohort 2, an interim assessment of PK and safety was conducted. Based upon the absence of a clinically significant drug interaction of CORT125281 on enzalutamide exposure, enrollment to the subsequent cohort was initiated to further evaluate the CORT125281 140 mg BID dose level without the enzalutamide lead-in. Seven patients have been enrolled to Cohort 3. One patient was not evaluable for DLTs due to disease progression during Cycle 1. Of the 6 remaining patients, no DLTs were observed and the dose was considered tolerable.

Twelve patients (100%) who have received at least 1 dose of CORT125281 in combination with enzalutamide reported greater than 1 TEAE. Five patients (42%) reported TEAEs of Grade 3 or greater considered related to CORT125281; the most frequent TEAE of Grade 3 or greater was fatigue (n=2; 17%). An alternative schedule (once daily [QD] dosing of CORT125281) is planned to optimize the biologically active dose prior to proceeding to the Phase 2 expansion cohorts.

CORT125281-602

In accordance with the study design, 6 healthy subjects received a single oral dose of [^{14}C]-CORT125281 360 mg (6 × 60-mg capsules). No TEAEs were reported in this study.

1.4 Enzalutamide

Enzalutamide (Xtandi®) is an AR inhibitor that has been shown to competitively inhibit androgen binding to AR and inhibit AR translocation and interaction with deoxyribonucleic acid (DNA) (see Summary of Product Characteristics [SmPC] and United States Package Insert [USPI] for Xtandi). Two Phase 3, randomized, double-blind clinical trials have demonstrated a survival benefit of enzalutamide in men with mCRPC. In the AFFIRM trial, men with mCRPC previously treated with docetaxel therapy (N=1199) were randomized to enzalutamide or placebo. Enzalutamide therapy resulted in an improvement in median overall survival of 4.8 months compared to placebo (hazard ratio [HR] 0.63: 95% confidence interval [CI], 0.53-0.75, P<0.001) (Scher et al. 2012b), with a consistent benefit observed across subgroups and secondary endpoints. In the Prevail trial, men with asymptomatic or minimally symptomatic mCRPC who had not received chemotherapy, abiraterone, or ketoconazole (N=1717) were randomized to enzalutamide or placebo. The study met its coprimary endpoints, with significant improvements for enzalutamide versus placebo in both progression-free survival and overall survival (overall survival HR 0.71; 95% CI 0.60-0.84) (Beer et al. 2014). Based on these studies, enzalutamide is approved for the treatment of patients with mCRPC.

The most common adverse reactions of enzalutamide (≥10%) are asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension and

dizziness/vertigo. Other important adverse reactions include falls, nonpathologic fractures, cognitive disorder, hypersensitivity, ischemic heart disease, and neutropenia. Seizure occurred in 0.5% of patients receiving enzalutamide in clinical studies. There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide. Enzalutamide should be permanently discontinued in any patient experiencing seizure or PRES during treatment (Xtandi USPI 2019).

CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. It is recommended to avoid strong CYP2C8 inhibitors, as they can increase the exposure to enzalutamide. CYP3A4 plays a minor role in the metabolism of enzalutamide. In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index should be avoided in patients receiving enzalutamide, as enzalutamide may decrease the plasma exposures of these drugs.

Gemfibrozil (600 mg BID) increased the area under the curve from 0 to infinity ($AUC_{0\text{-}inf}$) of enzalutamide and N-desmethyl enzalutamide (M2, the active metabolite of enzalutamide) by 2.2-fold with minimal effect on C_{max} (Xtandi USPI 2019). Gemfibrozil is converted by metabolism to gemfibrozil glucuronide, a strong, metabolism-dependent, inhibitor of CYP2C8 with a metabolism shifted IC_{50} of 1.8 µM for inhibition of CYP2C8. Gemfibrozil glucuronide is present in plasma at high levels, the total C_{max} and unbound C_{max} for gemfibrozil glucuronide are 20 µM and 2.3 µM, respectively (Ogilvie et al. 2006).

CORT125281 is a direct inhibitor of CYP2C8 (IC_{50} of 0.59µM). In contrast to gemfibrozil glucuronide, CORT125281 is high bound to human plasma proteins (>99.9%). Therefore, the available free fraction of gemfibrozil glucuronide (11.5%) is approximately 115-fold greater than the free fraction (<0.1%) of CORT125281. Therefore, at initial clinical doses of CORT125281 the free drug concentrations are not expected to cause a meaningful increase in exposure to enzalutamide and metabolites.

1.5 Rationale for Study Design and Dose Regimen

1.5.1 Design Considerations

This is the first study with CORT125281 in combination with enzalutamide in patients with mCRPC. This study is designed to assess the safety and tolerability, identify the recommended dose (RD), assess the PK and PD, and evaluate the preliminary efficacy of CORT125281 in combination with enzalutamide in patients with mCRPC.

This open-label study consists of 2 phases: a Dose-Determination Phase (Phase 1) and an Expansion Phase (Phase 2a) (Figure 2). In each part of the study, routine assessments of safety and tolerability using adverse event (AE) monitoring, measurement of vital signs, recording 12-lead electrocardiogram (ECG), physical examination and clinical laboratory safety tests, will be performed. Samples will be collected to determine standard PK parameters for CORT125281, enzalutamide, and their major metabolites. PK objectives are to characterize the PK profiles of CORT125281 and enzalutamide, and selected metabolites; and to assess the impact of CORT125281 on enzalutamide exposure (drug-drug interactions), and the effect of food on CORT125281 PK.

The Dose-Determination Phase is made up of 2 segments:

- In Dose-Determination Phase Segment 1 (open-label, twice daily CORT125281), patients will be evaluated by cohorts of 6 to 9 patients each; a flexible dose-escalation schedule (Table 7) will be used with dose-escalation decisions based on observed side effects and PK findings in the previous cohort, balanced against the animal pharmacology data with regard to antitumor activity (Verweij 2008). The purpose of Segment 1 is to better define the maximum tolerated dose (MTD)/biologically active doses of CORT125281 and for determination of the RD for BID dosing.
- In Dose-Determination Phase Segment 2 (double-blind, once daily CORT125281 under fed conditions), approximately 20 patients will be enrolled to determine the RD of CORT125281 for QD dosing under fed conditions.

Once both segments of the Dose-Determination Phase are complete, and the RD has been determined, patients will be enrolled into expanded safety cohorts to further evaluate the safety, tolerability, preliminary efficacy, and PK of CORT125281 in combination with enzalutamide and exploratory biomarkers of sensitivity or resistance. Based on the hypothesis that GR activation compensates for diminished AR signaling in CRPC treated with enzalutamide and facilitates cancer cell survival; the expansion cohorts will include:

- Abiraterone (Abi)-Resistant Cohort: Patients who have previously progressed while receiving abiraterone
- AR Antagonist (ARant)-Resistant Cohort: Patients who have previously progressed while receiving enzalutamide or other second-generation AR inhibitors.

The effect of food on CORT125281 PK will be assessed in 10 patients enrolled in the Expansion Phase. The expansion cohorts will be enrolled in parallel.

1.5.2 Rationale for Dose and Dose Regimen Selection

In Dose-Determination Phase Segment 1, the starting dose of CORT125281 will be 180 mg BID. The starting dose of CORT125281 is based on the following: (1) the anticipated safe exposure based on nonclinical toxicology and the ongoing Phase 1 SAD/MAD study in healthy subjects, (2) the biologically active dose range based on the rat cortisone-induced model of insulin resistance, and (3) the anticipated efficacious dose based on nonclinical mouse models (see Section 1.3.1 for a detailed summary).

At the time of initiation of this study, Study CORT125281-600 was an ongoing Phase 1 SAD/MAD study to assess the tolerability and PK of CORT125281 in the absence of other medications or comorbidities, define the pharmacologically active dose range, and assess the potential of CORT125281 for drug-drug interactions. No safety signals had been identified. Analysis of the available PK data from Study CORT125281-600 indicated that CORT125281 exposure is dose-proportionate from 120 to 720 mg based on both C_{max} and AUC_{0-24}. [redacted] Therefore, the predicted accumulation is minimal on repeat daily dosing. CORT125281 mean AUC_{0-24} following single-agent administration ranged from 217.4 ng•h/mL (40 mg dose) to 7199 ng•h/mL (720 mg dose). Based on the human PK data and modeling, a CORT125281 dose of 180 mg BID would result in an estimated AUC_{0-24} of 4200 ng•h/mL. The NOAEL following

28 days of oral gavage administration of CORT125281 to rats was 30 mg/kg/day in both sexes, with a corresponding exposure of 56,142 ng•h/mL in female rats, and 57,533 ng•h/mL in male rats (AUC_{0-24}). The estimated exposure of the 180 mg BID starting dose (4200 ng•h/mL) provides a 10-fold safety factor from the NOAEL exposure in the rat of 57,533 ng•h/mL.

Efficacy in nonclinical mouse models in combination with enzalutamide was observed at 20 mg/kg/day administered using the intraperitoneal route. In the mouse xenograft model, efficacy was observed at a minimum concentration (C_{min}) of 110 ng/mL; based on simulated human PK profiles, a CORT125281 dose of 360 mg BID would provide a 12-hour C_{min} of 137 ng/mL. In the cortisone-induced model of insulin resistance, the minimum anticipated biological effect level is 6 mg/kg/day in the rat with an estimated C_{max} of ~600 ng/mL (see Section 1.3.1.1.3). In Study CORT125281-600, a CORT125281 dose of 360 mg provided an observed mean C_{max} of 688 ± 120 ng/mL. The starting dose of CORT125281 of 180 mg BID is within the anticipated biologically effective dose range and will allow characterization of tolerability, PD, and preliminary efficacy across a range of doses during the Dose-Determination Phase.

The starting dose of enzalutamide in Dose-Determination Phase Segment 1 will be 160 mg QD. At initial clinical doses of CORT125281, the free drug concentrations are not expected to cause a meaningful increase in exposure to enzalutamide and metabolites; thus, the indicated dose of enzalutamide has been selected as the starting dose (Section 1.4; Xtandi USPI 2019). In Dose-Determination Segment 2, patients will continue taking enzalutamide at the patient's currently tolerated dose at baseline. In the Expansion Phase, patients will take enzalutamide 160 mg if not currently receiving enzalutamide or will take their currently tolerated dose of at baseline (if enzalutamide is ongoing from immediately preceding line of therapy).

In Dose-Determination Phase Segment 2, an alternative dosing strategy of upward titration from a starting dose of CORT125281 240 mg QD to 320 mg QD will be evaluated in a blinded manner. The effects of GCs and GC sensitivity can vary dramatically from individual to individual. Similarly, the PD effect of a GR antagonist for a given dose or exposure varies among individuals. In order to optimize the dose for each individual in the presence of by-patient variability in PK and sensitivity to GR antagonism and to minimize the exposure of individuals to potentially suboptimal doses, intra-patient dose escalation of CORT125281 is deemed appropriate.

Both the starting dose of CORT125281 240 mg QD under fed conditions and the highest dose of CORT125281 320 mg QD under fed conditions have been selected and deemed to be appropriate for Segment 2 based on the results from Dose-Determination Phase Segment 1 and the Phase 1 Study CORT125281-600 in healthy adult participants. Specifically, the plasma concentrations of CORT125281 observed in Segment 1 of this study, in combination with the decrease in CORT125281 C_{max} observed in Study CORT125281-600 following fed administration versus fasted administration, indicate that a targeted CORT125281 dose range of 240 mg to 320 mg administered QD under fed conditions will provide CORT125281 exposures (AUC_{0-24} and C_{max}) within the protocol-specified safety rule (Section 5.3) of 1.5-fold the previous dose level.

Additionally, the CORT125281 dose range to be evaluated in Segment 2 is 240 mg QD to 320 mg QD and is expected to yield pharmacodynamically active exposures resulting in GR antagonism, based on the PD data from Study CORT125281-600, in which subjects were

administered prednisone 25 mg with or without CORT125281. The biological activities of the GR agonist (prednisone) and antagonist (CORT125281) were assessed by measuring messenger ribonucleic acid (mRNA) expression of GC-modulated pathways in whole blood. A single 360-mg dose antagonized the biological activity of prednisone when administered with food. The same single CORT125281 360-mg dose under fasted conditions showed less antagonism. Food effects on the activity of prednisone alone were negligible. Given these data, it is anticipated that continuous dosing of CORT125281 240 to 320 mg under fed conditions will result in measurable GR antagonism.

The dose regimen selection of CORT125281 in combination with enzalutamide in subsequent cohorts and the selection of the RD for the expansion cohorts and future development will be based upon PK and safety data collected during the Dose-Determination Phase of the study and reviewed by the Data Review Committee (DRC).

1.5.3 Rationale for Patient Selection

Patients with mCRPC who have received no more than 2 prior lines of cytotoxic chemotherapy will be enrolled to this Phase 1/2a study. This population is consistent with the indication for enzalutamide. Patients who have previously received enzalutamide will be allowed to participate, as GR antagonism is intended to target one of the mechanisms of resistance to enzalutamide therapy.

1.6 Benefits and Risks

CORT125281 is a selective GR antagonist that is being developed for the treatment of mCRPC in combination with enzalutamide. GR activation has been identified as a mechanism of resistance to therapies that target the AR (Arora et al. 2013; Isikbay et al. 2014). The ability of a GR antagonist to restore sensitivity to enzalutamide has been reported (Arora et al. 2013) and GR depletion has been reported to delay CRPC formation in nonclinical models (Isikbay et al. 2014). In a castrated mouse xenograft model of CRPC, CORT125281 impaired tumor growth over castration alone, and the combination of CORT125281 and enzalutamide impaired tumor growth over enzalutamide alone. Thus, CORT125281 is anticipated to provide clinical benefit in CRPC in combination with enzalutamide.

The principal risk identified from the nonclinical data was to the male reproductive tract and included bilateral degeneration of the spermatocytes and spermatids and oligospermia/germ cell debris in the testes. This risk does not preclude the use of CORT125281 in the intended target population of male patients with CRPC. Potential adverse effects of CORT125281, based on the pharmacological effect of a GR antagonist, may include signs and symptoms consistent with excessive GR blockade. Patients with conditions that require chronic or frequent corticosteroids will be excluded. Based upon clinical data with other GR antagonists (mifepristone and CORT125134), potential risks of CORT125281 include nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, and musculoskeletal pain.

Based upon clinical data for other GR antagonists (such as mifepristone and relacorilant), potential risks of CORT125281 include nausea, fatigue, headache, arthralgia, vomiting, peripheral edema, and musculoskeletal pain. Within the Phase 1 Study CORT125281-600 in healthy subjects receiving multiple dosing with CORT125281, the most frequent

treatment-related TEAEs were in the following SOCs: gastrointestinal system disorders, ear and labyrinth disorders, nervous system disorders, and musculoskeletal and connective tissue disorders. Although the number of events is too small to determine an association with CORT125281, treatment-related gastrointestinal disorders and musculoskeletal and connective tissue disorders were reported only by subjects treated with CORT125281 and with a generally increasing incidence with dose. Thus, in this study, no additional potential risks of CORT125281 were identified. No patterns of TEAEs were observed in healthy subjects receiving single doses of CORT125281 (Studies CORT125281-600 and CORT125281-602).

In the current study, CORT125281 will be given in combination with enzalutamide. Enzalutamide has been demonstrated to have survival benefit in patients with CRPC (Xtandi USPI 2019 and Xtandi SmPC 2019). The most common adverse reactions of enzalutamide (≥10%) that occur more frequently (≥2% over placebo) in patients treated with enzalutamide are asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension (Xtandi USPI 2019) In general, enzalutamide is well-tolerated and enzalutamide-related AEs of Grade 3 or greater are uncommon. The most common AE is fatigue (34%36%), but this rarely reaches Grade 3 or greater. Seizure has been reported in patients receiving enzalutamide (<1%), primarily in patients with predisposing factors that could lower the threshold for seizure. Thus, patients at increased risk for seizure will be excluded from this study and medications that could lower the seizure threshold (such as olanzapine, prochlorperazine, or methylphenidate) should be avoided. Based upon the mechanism of action, enzalutamide and CORT125281 are not anticipated to have overlapping toxicities.

Patients will be closely monitored during the study; standard safety tests will be performed at regular intervals; and samples collected to determine standard PK parameters for CORT125281, enzalutamide, and their major metabolites. Concurrent therapy with strong inhibitors or inducers of CYP3A4 or CYP2C8 or with sensitive substrates of CYP3A4, CYP2C9, or CYP2C19 will be prohibited during the study treatment, consistent with the enzalutamide label and with consideration of potential drug-drug interactions between enzalutamide and CORT125281.

Although animal toxicity studies do not always predict the potential human toxicities of a new drug candidate, the completed GLP toxicity studies support the probable satisfactory tolerance of CORT125281 in the dose range to be investigated in this study.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the MTD and/or biologically active doses of CORT125281 in combination with enzalutamide to identify the RD for Phase 2 studies.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the safety and tolerability of CORT125281 in combination with enzalutamide
- Characterize the preliminary efficacy of CORT125281 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
- 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 CORT125281 and enzalutamide, when co-administered
- Determine the effect of food on the PK of CORT125281

2.3 Exploratory Objectives

Exploratory objectives of this study are to:

- Evaluate the effects of CORT125281 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 CORT125281 and enzalutamide by line of therapy and in specific sub-sets of disease, including:
  - GR positive versus GR negative, 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 analyses of exposure-response for measures of efficacy and changes in GC-modulated pathways, ACTH/cortisol, or other PD markers
- Assess the effect of the pharmacogenomics polymorphisms of the cytochrome P450 pathway on PK and PD parameters (Dose-Determination Phase Segment 1 only)
- Explore the effects of CORT125281 and enzalutamide on patient-reported outcomes (PRO) and quality of life (QoL)

3 STUDY DESIGN

3.1 Overall Design

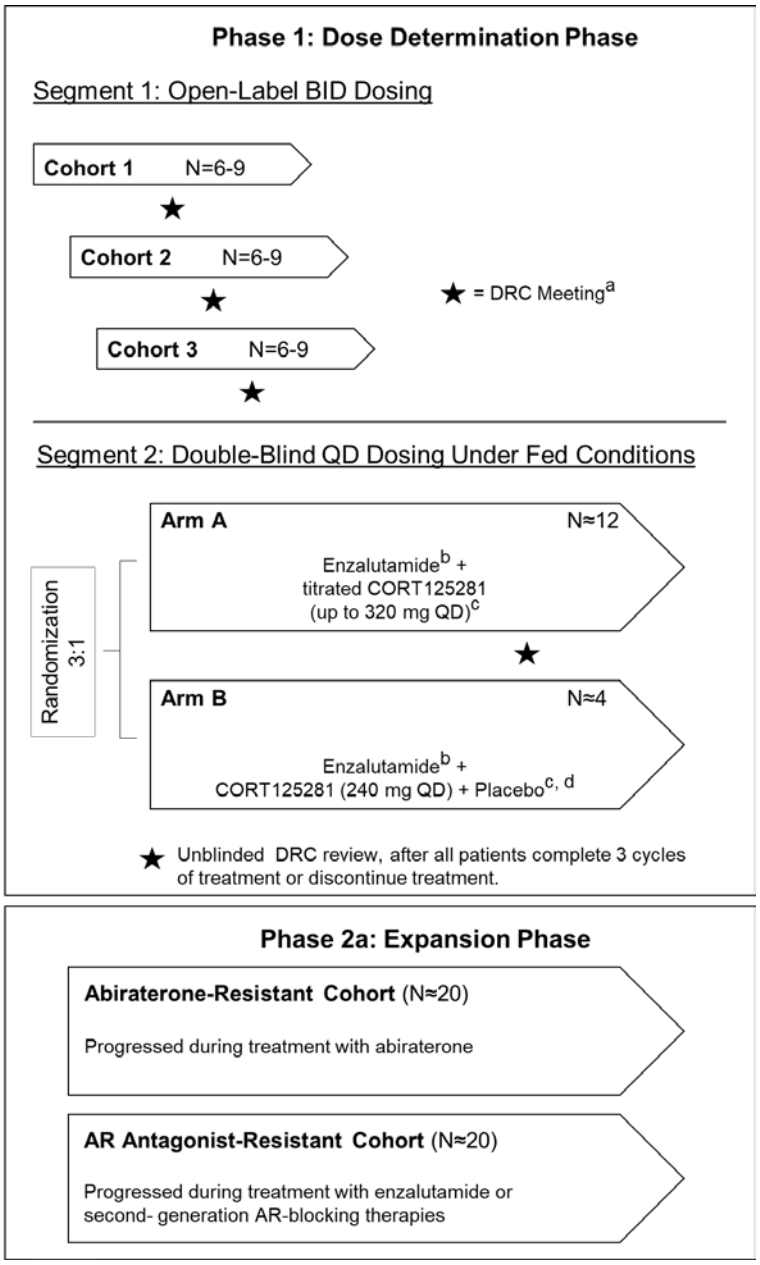
This is a Phase 1/2a, dose-determination and expansion study conducted in patients with mCRPC to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of CORT125281 in combination with enzalutamide; and to identify the RD.

The study consists of the following phases:

- Dose-Determination Phase (Phase 1):
  - Segment 1 (Open-Label, Twice Daily CORT125281): Patients enrolled in this segment will take CORT125281 BID in combination with enzalutamide QD. The starting dose in this segment of the study for CORT125281 is 180 mg BID, with subsequent dose cohorts to be determined based DRC review of tolerability and PK data. Enzalutamide will be administered at a starting dose of 160 mg QD, with subsequent dosing to be determined based upon PK.
  - Segment 2 (Double-Blind, Once Daily CORT125281 Under Fed Conditions): Patients in this segment will be randomized in a 3:1 ratio to Arm A (enzalutamide + titrated dose of CORT125281) and Arm B (enzalutamide + CORT125281 240 mg). All patients will take CORT125281 QD with food. Enzalutamide will be continued at the patient's currently tolerated dose through the Screening Period and the initiation of CORT125281. The DRC will review the frequency of dose-limiting toxicities (DLTs), the DLT rate (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 RD.
- Expansion Phase (Phase 2a, CORT125281 at the RD Under Fed Conditions): Once the RD has been determined in the Dose-Determination Phase, the following cohorts will be enrolled and treated with CORT125281 (with the RD regimen, under fed conditions) + enzalutamide. The DRC may elect to expand more than 1 dose level, if needed, to better define the RD:
  - Abi-Resistant Cohort: Patients who have progressed during treatment with abiraterone and no other AR-blocking therapies
  - ARant-Resistant Cohort: Patients who have progressed during treatment with enzalutamide or second-generation AR-blocking therapies.

The overall study design is presented in Figure 2.

Figure 2 CORT125281-601 Study 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 Phase Segment 1 once a minimum of 3 evaluable patients have completed the DLT-evaluation period (Section 5.4.1).

[b.] Enzalutamide will be 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 CORT125281 to a maximum dose of 320 mg QD under fed conditions (Arm A) or with placebo (Arm B) to maintain a CORT125281 dose of 240 mg QD under fed conditions (Table 8).

[d.] After the DRC meeting for Dose-Determination Segment 2, patients initially randomized to Arm B will have their CORT125281 dose escalated per the recommended Phase 2 regimen.

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
  - Dose-Determination Phase Segment 2: No Lead-In Period
  - Expansion Phase:
    - Food-Effect Subcohort: A single dose of CORT125281 under fasting conditions on Cycle 1 Day -7, and a single dose of CORT125281 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 (CORT125281 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 CORT125281 and enzalutamide are discontinued.
- **Follow-Up Period:** Patients will return for a Post-Treatment Follow-Up Visit (End-of-Treatment [EOT] +30 Days Visit) 30 days after their final dose of CORT125281 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.

PK, PD, safety, PRO and QoL evaluations will be performed throughout along with preliminary evaluations of antitumor activity as shown in the SoAs (Appendix A).

Dose evaluation will be guided by safety and PK profiles. Safety will be assessed by review of AEs, including DLTs; clinical laboratory tests, and vital signs. Anticancer activity will be evaluated using bone scan and computed tomography (CT) of the chest, abdomen, and pelvis, per Prostate Cancer Clinical Trials Working Group 3 (PCWG3).

The recommendations of the PCWG3 will be used to determine response (Scher et al. 2016). Tumor assessments will include ^{99}mTc-methylene diphosphonate radionucleotide bone scintigraphy and CT of the chest, abdomen, and pelvis within 28 days before the first dose of enzalutamide (for Dose-Determination Phase Segment 1) and/or CORT125281 (for Dose-Determination Phase Segment 2 and Expansion Phase) and at intervals of 8 weeks after the first dose of study treatment 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. Results will be documented in the electronic case report form (eCRF). Tumor assessments will be documented until disease progression. Documentation of overall survival including subsequent therapies with duration and response will continue every 4 months until 2 years from the date that the last patient enrolls in the study or until all patients have completed follow-up for radiographic disease progression (whichever is later).

3.1.1 Dose-Determination Phase (Phase 1)

3.1.1.1 Dose-Determination Phase Segment 1 (Open-Label)

Segment 1 of the Dose-Determination Phase is designed to determine DLTs, the MTD/biologically active doses, and the RD of CORT125281 administered daily in combination with 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 RD. Within each cohort, a sentinel group of 3 patients will be dosed initially, with a minimum of one day between Cycle 1 Day 1 for each patient. Dosing of the remaining patients with CORT125281 + enzalutamide will only proceed after satisfactory review of safety data (excluding laboratory safety tests) from the sentinel group collected up to 24 hours after the first dose of CORT125281 and enzalutamide. The DRC may make the recommendation to adjust the size of a cohort to more than 9 patients to further evaluate a given dose cohort, (eg, based on PK data or tolerability). Dose escalation and dose-finding procedures are described in Section 5.4.

Each patient will begin the Dose-Determination Phase Segment 1 with enzalutamide monotherapy. The DRC may elect to discontinue the Lead-In Period for future cohorts, once the RD of enzalutamide is determined.

After completion of the Lead-In Period, patients will begin the Combination Treatment Period and receive enzalutamide + CORT125281. CORT125281 will be dosed daily starting at 180 mg BID (Cohort 1). Subsequent patients will be enrolled and dosed similarly, with the doses of CORT125281 and enzalutamide for each cohort to be determined based upon the tolerability, PK, and dose escalation/de-escalation rules.

3.1.1.2 Dose-Determination Phase Segment 2 (Double-Blind)

Segment 2 of the Dose-Determination Phase is randomized and double blinded for dose titration with respect to CORT125281 in combination with enzalutamide.

Approximately 20 patients will be enrolled to achieve 16 DLT-evaluable patients randomized in a 3:1 ratio to receive CORT125281 in combination with enzalutamide either with the starting dose of CORT125281 240 mg QD with dose titration to 320 mg QD (N=12; Arm A) or with the starting dose of CORT125281 240 mg QD, without an increase of the active dose (N=4; Arm B), but with the addition of placebo capsules. All doses of CORT125281 should be taken with food.

3.1.2 Expansion Phase (Phase 2a)

Once the RD has been determined in the Dose-Determination Phase, the following cohorts will be enrolled in the Expansion Phase and treated with CORT125281 + enzalutamide according to the RD regimen. The DRC may elect to expand more than 1 dose level, if needed, to better define the RD.

- Abi-Resistant Cohort: Patients who have progressed during treatment with abiraterone and no other AR-blocking therapies (N≈20)
  - Food-Effect Subcohort: The effect of food on the PK of CORT125281 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 CORT125281 administered under fasting conditions
- Day 1: Single oral dose of CORT125281 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 CORT125281 PK

  Patients in the Abi-Resistant Cohort who do not participate in the food-effect study will not have a Lead-In Period.

- 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.

3.2 Number of Patients and Study Participation

3.2.1 Number of Patients

The number of patients in Dose-Determination Phase Segment 1 will depend on the number of dose cohorts assessed and the DLTs observed (6 to 9 patients per cohort).

Approximately 20 patients will be enrolled in Dose-Determination Phase Segment 2 to achieve 16 DLT-evaluable patients (Arm A: 12 patients, Arm B: 4 patients).

Approximately 40 patients will be enrolled in the Expansion Phase (20 patients in each cohort).

3.3 Definitions: End of Treatment, End of Study, and Study Duration

3.3.1 End of Treatment

The end of treatment is defined as the date on which the patient received his last treatment with either CORT125281 or enzalutamide, whichever is later.

3.3.2 End of Study

In accordance with European Union (EU) and US Food and Drug Administration (FDA) regulations, the end of study is defined as the date of last contact (by visit, telephone, or email) with any study patient. The Sponsor will ensure that the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the regulatory authority are notified that the study has finished according to Sponsor's Standard Operating Procedures (SOPs) and/or local or national regulations.

3.3.3 Study Duration

Patients will receive CORT125281 in combination with enzalutamide until reaching a protocol-defined event of disease progression, experiencing unmanageable toxicity, or until other treatment discontinuation criteria are met (Section 4.4.1). As per PCWG3, patients with an isolated PSA rise after an initial decline who show evidence of benefit should continue treatment until radiographic or clinical progression.

All patients will be followed for progression, information on subsequent anticancer therapies (start and end date and response) and survival.

3.4 Study Termination by Sponsor

If the Sponsor, Investigator, Study Monitor, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study site's participation should be terminated, this action may be taken after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

Study termination and follow-up will be performed in compliance with applicable regulations.

4 STUDY POPULATION

The following eligibility criteria are designed to select patients with mCRPC (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) and patients with mCRPC with rising PSA, defined as a 25% increase over nadir and an absolute value >1 ng/mL, based on 2 measurements at least 1 week apart, for whom the protocol treatment is considered appropriate. All relevant medical and nonmedical conditions will be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Able to understand the purpose and risks of the study; willing and able to adhere to scheduled visits, treatment plans, laboratory tests, and other study evaluations and procedures, and provide written informed consent.
2. Males ≥18 years of age at time of signing consent.
3. Histologically confirmed adenocarcinoma of the prostate with metastatic disease.
4. Dose-Determination Phase Segment 1 and Expansion Phase: Progressive disease as defined by PSA or imaging after most recent prior therapy. PSA ≥1 ng/mL, if a confirmed rise in PSA is the only indication of progression. Progression by PSA requires rising PSA over a previous reference value by at least 2 measurements obtained ≥1 week apart. PSA measurements can be collected during or after the most recent prior therapy.
5. Dose-Determination Phase Segment 2: Currently receiving enzalutamide with a rising PSA as follows:
    a. Rising PSA: 25% increase over nadir and an absolute value of >1 ng/mL by at least 2 measurements obtained ≥1 week apart. PSA measurements can be collected during or after the most recent prior therapy.
    b. Patients must have received enzalutamide for a minimum of 12 weeks and be on stable doses of enzalutamide ≥80 mg QD for at least 4 weeks prior to Cycle 1 Day 1.
        - Patients will continue enzalutamide without interruption during the Screening Period (no wash-out period).
        - This will be the enzalutamide starting dose for combination with CORT125281 beginning on Cycle 1 Day 1.
    c. M0 disease is allowed.
6. Expansion Phase: Patients must have progressed while receiving an androgen-directed therapy as follows:
    a. Abi-Resistant Cohort: Patients must have progressed during treatment with abiraterone.
    b. ARant-Resistant Cohort: Patients must have progressed during treatment with enzalutamide or second-generation AR-blocking therapies. Patients progressing on enzalutamide immediately prior to enrolling in this study must be on stable doses of enzalutamide. These patients will continue enzalutamide without interruption during the Screening Period (no wash-out period required).
7. Baseline tumor assessment performed within 28 days prior to the first dose of study treatment (CORT125281 and/or on-study enzalutamide, whichever is earlier).

8. Prior surgical or chemical castration with serum testosterone <1.7 nmol/L (50 ng/dL). If the method of castration is use of a luteinizing hormone-releasing hormone (LHRH) analogue, there must be a plan to maintain effective LHRH analogue treatment for the duration of the trial.
9. If bisphosphonates or denosumab were started within 4 weeks prior to first dose of CORT125281, then Grade 2 or greater toxicities were not observed.
10. Consent to provide paired tissue biopsies, obtained within 6 weeks prior to the first study dose of study treatment (CORT125281 and/or on-study enzalutamide, whichever is earlier) and at Cycle 2 Day 1 (Window of within 14 days prior to Cycle 2 Day 1 is acceptable. Soft tissue biopsy is preferred, when possible).
    - A sufficient number of patients will be enrolled to provide paired biopsies in approximately 4 patients enrolled per cohort in Dose-Determination Phase Segment 1, approximately 10 patients (total) in Dose-Determination Phase Segment 2, and approximately 10 patients per cohort in the Expansion Phase. For these patients, providing paired tissue biopsies is mandatory. Consent to provide biopsies will be optional in the remaining patients. The requirement for biopsies will be communicated to each patient during the enrollment process. Inability to obtain biopsy tissue will not impact the patient's ability to participate in the study.
    - Patients may also consent to provide on-study optional biopsies (1) obtained during procedures that are conducted as part of the patient's standard treatment; and/or (2) at the time of disease progression.
11. Consent to provide mandatory pharmacogenomic blood sample (Dose-Determination Phase Segment 1 only).
12. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
13. Adequate baseline organ function within 14 days prior to the first dose of study treatment (on-study enzalutamide and/or CORT125281, whichever is earlier):
    a. Absolute neutrophil count (ANC) ≥1,500/µL, platelet count ≥100,000/µL, and hemoglobin ≥9 g/dL (NOTE: patients may not have received any growth factors or blood transfusions within 7 days prior to the hematologic laboratory values obtained during the Screening Period)
    b. Total bilirubin ≤1 × the upper limit of normal (ULN), and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN. Patients with Gilbert's syndrome may have bilirubin >1.5 × ULN if there is no evidence of hepatobiliary obstruction or hepatic dysfunction
    c. Creatinine ≤ULN (National Cancer Institute Common Terminology for Adverse Events [NCI-CTCAE] Grade 0); if creatinine >ULN: creatinine clearance >60 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) Study equation (Levey et al. 1989)
    d. Albumin ≥3.0 g/dL (≥30 g/L)
    e. Activated partial thromboplastin time (aPTT) must be ≤1.5 × ULN and international normalized ratio (INR) <1.5. Patients on anticoagulant therapy will have an appropriate aPTT and INR as determined by the Investigator
14. Patients receiving systemic corticosteroids greater than 2 weeks in duration within 3 months of study entry or with clinical evidence of adrenal insufficiency must have adequate adrenal function as evidenced by a morning plasma cortisol concentration of

greater than or equal to 10 µg/dL or a plasma cortisol response to an ACTH (cosyntropin) stimulation test that is deemed clinically normal (value of greater than 18 µg/dL).

15. If a patient engages in sexual intercourse with a woman of childbearing potential, a condom with spermicide and another form of birth control must be used during and for 100 days after the final dose of study treatment (CORT125281 or enzalutamide, whichever is later). Acceptable methods of birth control (to be used in conjunction with a condom and spermicide) are:
    a. Established use of oral, injected or implanted hormonal methods of contraception
    b. Placement of an intrauterine device or intrauterine system
    c. Barrier methods of contraception: occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
    d. Tubal ligation
    e. Vasectomy or other surgical castration prior to initial Screening

    A condom is required during and for 100 days after completing treatment with enzalutamide if a patient is engaged in sexual activity with a pregnant woman. Patients must also agree to avoid sperm donation during the study and for at least 100 days after the final treatment administration.
16. Able to swallow and retain oral medication without uncontrolled nausea or emesis.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will not be permitted entry to the study:

1. Received chemotherapy, non-palliative radiotherapy, immunotherapy, or any investigational cancer therapies within 21 days prior to the first dose of CORT125281, or treatment with such therapies is planned during protocol treatment. Concomitant anticancer therapy is not permitted during the enzalutamide Lead-In Period during Dose-Determination Phase Segment 1.
2. More than 2 prior cytotoxic chemotherapy regimens for the treatment of mCRPC.
3. The Dose-Determination and Expansion Phases will exclude patients for the following:
    - Dose-Determination Phase (Segment 1 only):
        - Progressed during treatment with enzalutamide prior to Cycle 1 Day -28 (only applies to patients receiving enzalutamide lead-in) or
        - Received prior second-generation anti-androgen and require urgent disease response or stabilization
    - Expansion Phase, Abi-Resistant Cohort:
        - Received prior therapy with enzalutamide or
        - Received prior second-generation anti-androgen and require urgent disease response or stabilization
    - Expansion Phase, ARant-Resistant Cohort: Require urgent disease response or stabilization
4. Ongoing or anticipated therapy with hormone therapy (other than LHRH analogue), including any dose of megestrol acetate (Megace), finasteride (Proscar), dutasteride (Avodart) or received abiraterone within 28 days prior to the first dose of CORT125281.

5. Received palliative radiotherapy within 2 weeks prior to the first dose of study treatment (on-study enzalutamide and/or CORT125281, whichever is earlier). If palliative radiation therapy included the pelvis, a minimum of 4 weeks is required between palliative radiotherapy and the first dose of CORT125281.
6. Contraindication or precaution for enzalutamide including history or risk factors for seizures; fructose intolerance; PRES, or discontinuation of prior treatment with enzalutamide due to toxicity.
7. Parenchymal brain metastases.
8. Any clinically significant uncontrolled condition that may increase the risk to the study patient or that the Investigator considers places the patient at unacceptable risk, including but not limited to the following:
    a. Myocardial infarction resulting from acute coronary syndrome or transient ischemic attack with 12 months of enrollment
    b. Acute coronary syndromes (including unstable angina), coronary angioplasty, stenting, or bypass grafting within the past 6 months prior to enrollment, Class III or IV heart failure as defined by the New York Heart Association functional classification
    c. Recent history of or risk factors for torsades de pointes, including marked baseline prolongation of QT interval (eg, repeated demonstration of a corrected QT [QTc] interval >450 milliseconds using Fridericia's formula [QTcF] or need for concomitant medication associated with QT prolongation; refer to https://www.crediblemeds.org/)
    d. Uncontrolled hypertension: Sustained systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg; patients will be considered eligible if hypertension is treated and controlled during Screening
    e. Active infection requiring IV anti-infective treatment
    f. Human immunodeficiency virus (HIV) or current chronic/active infection with hepatitis C virus or hepatitis B virus, including:
        i. Patients with chronic or active hepatitis B as diagnosed by serologic tests are excluded from the study. In equivocal cases, hepatitis B or C polymerase chain reaction may be performed and must be negative for enrollment.
    g. Active autoimmune disease requiring systemic treatment
    h. Alcohol or other substance abuse or cirrhosis
9. Received herbal products or alternative therapies that may decrease PSA levels or that may have hormonal anti-prostate cancer activity (eg, saw palmetto, PC-SPES, PC-HOPE, St. John's wort, selenium supplements, grape seed extract) within 21 days of study treatment initiation or plans to initiate treatment with these products/alternative therapies during the entire duration of the study.
10. Received systemic GCs within 21 days prior to the first dose of CORT125281, or requirement for chronic or frequently used systemic or inhaled GCs for medical conditions (eg, rheumatoid arthritis, immunosuppression after organ transplantation). Short courses (≤5 days) for non-cancer-related reasons are allowed if clinically required (such as prophylaxis for CT).
11. Concurrent therapy with strong inhibitors or inducers of CYP3A4 or CYP2C8 or with sensitive substrates of CYP3A4, CYP2C9, or CYP2C19. For patients currently receiving strong CYP3A4 or CYP2C8 inducers, a minimum wash-out period of 21 days

is required prior to initiating the first day of CORT125281. For patients currently receiving strong CYP3A4 or CYP2C8 inhibitors, a minimum wash-out period of 14 days is required prior to initiating the first dose of CORT125281. Prohibited medications are not permitted during the enzalutamide Lead-In Period during Dose-Determination Phase Segment 1, as per protocol Section 5.9.2.
   - Co-administration of enzalutamide with warfarin will not be exclusionary. If co-administration of warfarin cannot be avoided, conduct additional INR monitoring
   - Refer to Appendix C for examples of prohibited concomitant medications and foods

12. Toxicities of prior therapies (except alopecia) that have not resolved to NCI-CTCAE of Grade 1 or less.
13. Any other concurrent cancer or a history of another invasive malignancy within the last 3 years that has a likelihood of recurrence of >30% within the next 5 years. Adequately treated non-melanoma skin cancers or non-muscle invasive urothelial cancer or other tumors curatively treated with no evidence of disease are permissible.
14. Concurrent treatment on other Phase 1, 2, or 3 investigational treatment studies for the treatment of prostate cancer.

4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

4.4 Patient Discontinuation of Treatment or Study Completion/Withdrawal

Patients will be informed before study entry that they are free to discontinue study treatment and to withdraw from the study treatment at any time and for any reason. Patients will also be informed that, if they withdraw, they can ask the Investigator to destroy any identifiable samples taken from them.

4.4.1 Patient Discontinuation of Study Treatment

Study treatment will be discontinued in any of the following occurrences:

- Progressive disease. If the patient is experiencing overall clinical benefit, the patient may be allowed to remain on the study. Both the Medical Monitor and the Investigator must agree that this is appropriate for the patient.
- Unmanageable toxicity.
- Request for early discontinuation or withdrawal of consent by the patient.
- The Investigator decides it is in the patient's best interest to discontinue treatment and/or participation in the study. Reasons may include the following:
  - The patient requires prohibited medications or initiates treatment with another drug for treating prostate cancer
  - The patient is not adherent to the protocol

If a patient discontinues CORT125281, enzalutamide will be continued per the guidelines provided in Section 5.7.1.1. If a patient discontinues enzalutamide, CORT125281 will also be discontinued.

Patients who discontinue study treatment for reasons other than withdrawal of consent (eg, AE, Investigator decision) will undergo a Post-Treatment/ EOT Visit and EOT +30 Days Visit, and will be followed for progression and survival.

4.4.2 Patient Withdrawal from Study/Study Completion

Withdrawal from the study (including all follow-up assessments) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the patient
- Patient is lost to follow-up
- Study termination by Sponsor
- Death

If a patient withdraws from the study, the Investigator should complete and report the observations as thoroughly as possible up to the date of withdrawal and the primary reason for withdrawal. For patients who withdraw consent to participate in the study, every effort should be made to determine whether the withdrawal of consent was related to an AE or a specific aspect of the study.

The Investigator will ask all withdrawn patients to consent to a follow-up examination, to check that they have come to no harm as a result of taking part in the study. Provided that patients agree, they will undergo the standard medical examination and laboratory tests that they would have undergone had they completed it.

If a patient withdraws from the study without meeting study endpoints, the Investigator will immediately (within 48 hours after discontinuation) notify the Sponsor.

4.5 Restrictions During the Study

If a patient engages in sexual intercourse with a woman of childbearing potential, a condom with spermicide and another form of birth control must be used during and for 100 days after the final dose of study treatment with (CORT125281 or enzalutamide, whichever is later). The following are acceptable forms of contraception (to be used with a condom with spermicide):

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device or intrauterine system
- Barrier methods of contraception: occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Tubal ligation
- Vasectomy or other surgical castration prior to initial Screening

A condom is required during and for 100 days after treatment with enzalutamide if a patient is engaged in sexual activity with a pregnant woman. Patients must also agree to avoid sperm donation during the study and for at least 100 days after the final treatment administration.

5 STUDY TREATMENTS AND MANAGEMENT

Study drug is defined as CORT125281. The co-administered drug is defined as enzalutamide.

Study treatment is defined as CORT125281 and/or enzalutamide, administered according to the protocol.

5.1 Study Drug (CORT125281) and Placebo

CORT125281 and placebo appearance, dose strength (active), administration, packaging, labeling, and storage, are described in Table 1. The starting dose of CORT125281 is described in Section 1.5.2.

Table 1 Study Drug and Placebo: Formulation, Administration, Packaging, and Storage

Specifications	Study Drug and Placebo	
	CORT125281	**Placebo**
Description	• CORT125281 hard-shell capsules, 20 mg and 60 mg • CORT125281 softgel capsules, 40 mg	Placebo for CORT125281 softgel capsule
Supplied/Unit Dose Strength	<u>CORT125281 hard-shell capsules:</u> Two strengths of study drug will be provided as banded, hard-shell gelatin capsules: • 20 mg (White, Size 3 capsule) • 60 mg (White, Size 0 capsule)	Not applicable (no hard-shell gelatin placebo)
	<u>CORT125281 softgel capsules:</u> One strength of study drug will be provided as softgel capsules: • 40 mg (Opaque brown, oval softgel capsule) NOTE: Existing patients currently administered CORT125281 20-mg and 60-mg hard-shell gelatin capsules will continue with their dosing until their supply of hard-shell gelatin capsules are depleted; at that time the patient will be switched to CORT125281 40-mg softgel capsules at similar doses/exposures to their currently tolerated dose, or per the recommended Phase 2 regimen.	Placebo for CORT125281 40-mg softgel capsule matches the appearance of the CORT125281 40-mg softgel capsules.
Administration	Oral Swallow capsules whole. Do not chew, dissolve, or open the capsules.	Oral Swallow capsules whole. Do not chew, dissolve, or open the capsules.

Specifications	Study Drug and Placebo	
	CORT125281	**Placebo**
Packaging and labeling	CORT125281 20-mg and 60-mg hard-shell capsules will be provided in bottles containing 30 capsules. CORT125281 40-mg softgel capsules will be provided in: • Bottles with open label containing 30 capsules • Bottles with blinded labels containing 21 capsules	Placebo for CORT125281 40-mg capsules will be provided in bottles with blinded labels containing 21 capsules.
Storage	Store as follows: • In a secure location • At 20°C to 25°C (68°F to 77°F) with excursions allowed between 15°C and 30°C (59°F and 86°F) • Out of reach and sight of children	Store as follows: • In a secure location • At 20°C to 25°C (68°F to 77°F) with excursions allowed between 15°C and 30°C (59°F and 86°F) • Out of reach and sight of children
Packager	Corcept Therapeutics	Corcept Therapeutics

5.2 Non-Investigational Medicinal Agent (Enzalutamide)

Enzalutamide description, packaging, and storage are described in Table 2. The starting dose of enzalutamide is described in Section 1.5.2.

Table 2 Enzalutamide: Formulation, Administration, Packaging, and Storage

Specifications	Enzalutamide (Xtandi®) [a]
Description	Xtandi® (enzalutamide) capsule
Supplied	White to off-white oblong soft gelatin capsules imprinted with black ink with "ENZ"
Unit dose strength	40 mg enzalutamide/capsule
Dose levels	• Dose-Determination Phase Segment 1: Starting dose of 160 mg QD, with subsequent dosing to be determined based upon PK • Dose-Determination Phase Segment 2: At the patient's currently tolerated dose at baseline • Expansion Phase: 160 mg QD if not currently receiving enzalutamide or at the patient's currently tolerated dose at baseline if ongoing from the immediately preceding line of therapy
Administration	Oral Swallow capsules whole. Do not chew, dissolve, or open the capsules.
Packaging and labeling	Commercially available enzalutamide, 40 mg capsules will be provided by the site in bottles containing 120 capsules

Specifications	Enzalutamide (Xtandi®) [a]
Storage	Store as follows: • In a secure location • In their original bottles • At 20°C to 25°C (68°F to 77°F), in a dry place, tightly closed. Excursions will be permitted from 15°C to 30°C (59°F to 86°F) • Keep this and all medications out of the reach of children
Packager	Astellas Pharma US Inc.

5.3 Timing of Study Treatment Administration

5.3.1 Dose-Determination Phase Segment 1 (Twice-Daily Dosing of CORT125281)

Patients in Dose-Determination Phase Segment 1 will take CORT125281 BID beginning on Cycle 1 Day 1 (every 12 hours ±3 hours) unless otherwise specified (Table 3), with the first dose occurring in the morning. It is recommended that if a patient misses a scheduled dose of CORT125281 and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the patient should not take the missed dose, but should wait and take the next regularly scheduled dose. A window of at least 6 hours should be maintained between doses.

Alternative dosing schedules for CORT125281 dosing may be evaluated. If alternative schedules are evaluated, the total daily dose of CORT125281 will not exceed that projected to provide an exposure (AUC_{0-24} and C_{max}) of 1.5-fold the previous dose level.

Enzalutamide will be taken once a day, starting on Day -28 (Lead-In Period) and continuing through the combination period (Table 3) and, unless otherwise specified, should be taken in the morning. After completion of Cycle 2, enzalutamide may be dosed in the evening, if preferred by the patient or recommended by the Investigator.

The treatment schema for Dose-Determination Phase Segment 1 is summarized in Table 3.

Table 3 Treatment Schema for Dose-Determination Phase Segment 1

Cycle Study Treatment	Lead-In Period Days –28 to -1	Combination Treatment Period Days 1 to 28
Cycle 1		
CORT125281	No dose taken	Twice a day
Enzalutamide	Once a day	Once a day
Cycle 2 – End		
CORT125281	N/A	Twice a day
Enzalutamide	N/A	Once a day

N/A, not applicable.

5.3.2 Dose-Determination Phase Segment 2 (Once-Daily Dosing of CORT125281)

Patients in Dose-Determination Phase Segment 2 will take CORT125281 QD beginning on Cycle 1 Day 1 and enzalutamide QD (continuing from the previous regimen). CORT125281 should be taken with the evening meal, unless otherwise specified for PK/PD assessments. The window between CORT125281 doses should be ≥18 hours from the previous dose. Patients participating in this part of the study will not have a Lead-In Period.

To help ensure ≥18 hours from the previous CORT125281 dose are maintained between doses and to allow PK/PD assessments to be taken in the clinic during normal hours, Table 4 provides recommended dosing times. After Cycle 2, all doses of CORT125281 should be taken in the evening around the same time each day, with the evening meal. Enzalutamide should be taken once a day at a consistent time of day (the time of day is per the Investigator's discretion).

Table 4 Example Treatment Times for Dose-Determination Phase Segment 2

Day	CORT125281 Administration					
	Cycle 1		Cycle 2		Cycle 3 and Subsequent Cycles	
	Example Dosing Time	Time Since Prior Dose	Example Dosing Time	Time Since Prior Dose	Example Dosing Time	Time Since Prior Dose
1[a]	10:00-12:00	N/A	11:00-12:00	18 h	Any time in the evening with the evening meal	≥18 h
2-13	18:00	24-32 h	18:00	24-31 h		
14	17:00-18:00	23-24 h	17:00-18:00	23-24 h		
15[a]	11:00-12:00	18 h	11:00-12:00	18 h		
16-27	18:00	24-31h	18:00	24-31 h		
28	17:00-18:00	23-24 h	17:00-18:00	23-24 h		

h, hour; N/A, not applicable; QD, once daily.

Note: Time of administration is displayed in international format. The example times are provided as a suggestion but may not match the actual dosing times, as long as CORT125281 is always administered with at least 18 hours between each once-daily dose. Thus, on days with PK/PD assessments, dosing may occur in the morning so long as an 18-hour window is maintained.

[a] Both CORT125281 and enzalutamide will be administered in the clinic on this day, at the same time, if PK/PD assessments will be collected.

5.3.3 Expansion Phase

In the Expansion Phase Food-Effect Subcohort, patients will receive a single dose of CORT125281 under fasting conditions on Cycle 1 Day -7 (Lead-In Period), and a single dose of CORT125281 30 minutes after a standard breakfast on Cycle 1 Day 1. After this, patients will be treated with CORT125281 BID and enzalutamide QD for the remainder of the Combination Treatment Period.

The treatment schema for patients in the Food-Effect Subcohort of the Expansion Phase is summarized in Table 5.

Table 5 Treatment Schema for Expansion Phase: Food-Effect Subcohort

Cycle Study Treatment	Lead-In Period		Combination Treatment Period	
	Day –7	Day –6 to Day –1	Day 1	Days 2 to 28
Cycle 1				
CORT125281	Single morning dose	No dose taken	Single morning dose	Twice a day
Enzalutamide	No dose taken	No dose taken	No dose taken	Once a day
Cycle 2 – End				
CORT125281	N/A	N/A	Twice a day	Twice a day
Enzalutamide	N/A	N/A	Once a day	Once a day

N/A, not applicable.

Patients who are not in the Food Effect Subcohort will not have a Lead-In Period. These patients will initiate treatment with both CORT125281 BID and enzalutamide QD on Cycle 1 Day 1.

The treatment schema for non-food-effect patients in the Expansion Phase is summarized in Table 6.

Table 6 Treatment Schema for Expansion Phase: Non-Food-Effect Patients

Cycle Study Treatment	Combination Treatment Period
	Days 1 to 28
Cycle–1 - End	
CORT125281	Twice a day
Enzalutamide	Once a day

N/A, not applicable.

5.4 Dose-Determination Process

5.4.1 Dose-Determination Phase Segment 1 (Open-Label)

Dose-finding decisions including selection of dose levels for cohorts, determination of the MTD, RD, and stopping enrollment, as applicable, will be performed by the DRC. The key principles guiding DRC recommendations for dose levels in dose-finding are to ensure that patients receive treatment at therapeutic exposures and to sequentially increase the dose of CORT125281 in combination with enzalutamide as tolerated.

Dose escalation or de-escalation will occur only after review of data from each cohort by the DRC. All available data from patients receiving study drug will be used in dose escalation decisions. In addition, AEs occurring after the first cycle and ongoing PK assessment will be considered in dose escalation decisions.

There will be a 28-day DLT-evaluation period (from the first dose of CORT125281 through the completion of Cycle 1). The DLT-Evaluable Population will include all patients in the Dose-Determination Phase cohorts who receive at least 1 dose of CORT125281 and fulfill at least one of the following:

- Complete at least 28 days of continuous treatment with CORT125281 + enzalutamide and received at least 75% of the study regimen
- Experience a DLT

Patients who are non-evaluable for DLTs will include the following:

- Received <75% of the study regimen for reasons other than toxicity
- Patients who withdraw from the study prior to completion of Cycle 1 for reasons other than toxicity (eg, lost to follow-up, withdrawal of consent, or disease progression)

Patients who are non-evaluable for DLTs will be allowed to continue in the study and receive CORT125281 in combination with enzalutamide. Patients who experience toxicities requiring dose modification during the Lead-In Period may continue the study, with appropriate dose modification of enzalutamide and agreement of the Investigator and Medical Monitor but will be considered non-evaluable for DLTs. Patients who are non-evaluable for DLTs may be replaced to allow a sufficient number of evaluable patients per cohort.

A minimum of 3 evaluable patients in each cohort must complete 28 days of continuous combination treatment with enzalutamide and CORT125281 and have safety data reviewed by the DRC (described in Section 9.9) prior to proceeding to the next dose level. If <33% of the DLT-evaluable patients have experienced a DLT, then enrollment may proceed in the next cohort. If ≥33% of the DLT-evaluable patients have experienced a DLT in a cohort, (with a minimum of 6 evaluable patients if 1 DLT is observed), the previous dose will be considered for the MTD or dose de-escalation will occur by approximately 20% from the current dose (with rounding allowed to account for available capsule strengths [Table 1]).

The CORT125281 dose for Cohort 1 of the Dose-Determination Phase Segment 1 will be 180 mg BID. Dose escalation of CORT125281 will initially be in up to doubling steps until any DLT or Grade 2 toxicity attributed to CORT125281 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. The dose-escalation scheme is presented in Table 7.

Table 7 CORT125281 Dose Escalation and Reduction Scheme for Dose-Determination Segment 1

Dose Level	CORT125281 Dose (mg/day)
−1	280 mg/day
1 (Starting dose)	360 mg/day
Subsequent cohorts, until any DLT or Grade 2 toxicity attributed to CORT125281 is reported	Increase the dose by up to 100% (double the dose in the previous dose level)
Following any dose level with a DLT or Grade 2 toxicity attributed to CORT125281	Increase the dose in the most recent dose level by ≤50%

DLT, dose-limiting toxicity.

The enzalutamide dose for Cohort 1 of Dose-Determination Phase Segment 1 will be 160 mg daily during the Lead-In and Combination Treatment Periods. The enzalutamide dose in subsequent cohorts may be increased or decreased based on safety, PK, and tolerability. The Mean Ratio enzalutamide (ENZ) + M2 is the ratio of enzalutamide + M2 metabolite exposure concurrently administered with CORT125281 on Cycle 2 Day 1 divided by enzalutamide + M2 metabolite exposure on Cycle 1 Day -1. The Mean Ratio ENZ + M2 will be considered when assessing the effects of potential drug-drug interactions and determining the dose of enzalutamide for each cohort. While the DRC will consider the totality of the data and the variability that may occur with the small sample size in making their recommendations, a Mean Ratio ENZ + M2 <0.75 or >1.4 will be considered indicative of a notable interaction and support increasing or decreasing the dose of enzalutamide accordingly to achieve target exposures to approximate enzalutamide 160 mg daily.

5.4.2 Dose-Determination Phase Segment 2 (Double-Blind)

In Segment 2, all patients will start treatment with CORT125281 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 CORT125281. Beginning on Cycle 1 Day 16, the dose of the investigational agent will be increased in 40-mg increments every 2 weeks, as tolerated, with either CORT125281 (Arm A; N=12) to a maximum dose of CORT125281 320 mg QD or with placebo (Arm B; N=4) (Table 8). If any planned dose escalation is postponed due to transient intolerable Grade 2 toxicity or scheduling conflicts (delays not due to toxicity), the dose may be escalated within 14 days of the planned escalation.

- Arm A (N=12): CORT125281 240 mg QD under fed conditions with upward dose titration in combination with enzalutamide. CORT125281 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 8).
  - Cycle 1 Day 1: CORT125281 240 mg QD
  - Cycle 1 Day 16 (+14-day window): CORT125281 280 mg QD
  - Cycle 2 Day 2 to Cycle 2 Day 16 (+14-day window): CORT125281 320 mg QD

- Arm B (N=4): CORT125281 240 mg QD under fed conditions, with an increase in the number of placebo capsules every 2 weeks (+14-day window) (Table 8).
  - Cycle 1 Day 1: CORT125281 240 mg QD
  - Cycle 1 Day 16 (+14-day window): CORT125281 240 mg QD
  - Cycle 2 Day 2 to Cycle 2 Day 16 (+14-day window): CORT125281 240 mg QD

Table 8 CORT125281 Upward Dose Titration for Dose-Determination Phase Segment 2

Dose Level	Resulting CORT125281 Dosage (QD)		Open-Label Bottle (CORT125281)	Blind-Label Bottle (CORT125281 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 CORT125281 dose 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 CORT125281 (Section 5.7).
[a] Note: The blind-label bottle contains blinded capsules (CORT125281 [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 AEs considered related to either CORT125281 or enzalutamide and DLTs.

The DLT-evaluation period will extend from the first dose of CORT125281 through the completion of Cycle 3. The DLT-Evaluable Population will include all patients in Segment 2 who received at least 1 dose of CORT125281 and fulfilled at least 1 of the following:

- Completed 3 cycles of treatment with CORT125281 + enzalutamide and received at least 75% of the study regimen
- Experience a DLT

Patients who are non-evaluable for DLTs will include the following:

- Received <75% of the study regimen for reasons other than toxicity
- Patients who withdraw from the study prior to completion of Cycle 3 for reasons other than toxicity (eg, lost to follow-up, withdrawal of consent, or disease progression)

Patients who are non-evaluable for DLTs will be allowed to continue in the study and receive CORT125281 in combination with enzalutamide. Patients who are non-evaluable for DLTs may be replaced to allow a sufficient number of patients to evaluate DLTs (Section 9.4.1).

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 (number of DLTs in DLT-evaluable patients 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 RD.

If the DLT rate for the regimen is ≥33%, alternative titration schemes may be considered as the regimen for the RD, 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 RD, patients assigned to Arm B who have not experienced dose reductions due to toxicity will then escalate the CORT125281 dose per the recommended upward titration regimen.

5.5 Definition of Dose-Limiting Toxicities

DLTs will be recorded during the DLT-evaluation period (first dose of CORT125281 through completion of Cycle 1 for Segment 1, and first dose of CORT125281 through completion of Cycle 3 for Segment 2). A DLT is defined 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 (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 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 or ALP 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 >3 × ULN with concomitant total bilirubin of >2 × 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

Overall tolerability and DLTs occurring after the DLT-evaluation period will be considered by the DRC for the dose escalation decisions.

5.6 Maximum Tolerated Dose

The MTD for CORT125281 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 CORT125281 prior to reaching MTD based upon reliable evidence of GR antagonism and assessment of exposure-response for PD, tolerability, and efficacy. The RD of CORT125281 in combination with enzalutamide will take into account overall tolerability, PD markers of target engagement, and PK. The RD will always be ≤MTD.

5.7 Dose Modifications or Delays

If a patient experiences an AE that results in a delay in starting a cycle or requires that study regimen is delayed or interrupted during a cycle, the patient will complete the planned activities per the SoA (Appendix A) until resuming treatment. All toxicities, with the exception of non-treatment-related, clinically insignificant laboratory abnormalities, should be resolved to Grade 1 or baseline prior to initiation of a new cycle of therapy.

5.7.1 CORT125281 Dose Modification or Delay

If a patient experiences a toxicity of Grade 3 or greater, or an intolerable side effect, withhold enzalutamide and CORT125281 dosing for 1 week or until toxicity improves to Grade 1 or less, or to the patient's baseline. If the toxicity is attributed to CORT125281, resume CORT125281 at a reduced dose.

In Dose-Determination Phase Segment 1, the CORT125281 dose will be reduced to the next lower dose level as indicated in Table 7, or at least by 25% if the dose is below Dose Level -1.

In Dose-Determination Phase Segment 2, the CORT125281 dose will be reduced in 40-mg increments from the current dose level, without unblinding the patient's treatment assignment (exceptions noted in Section 5.12.2.1), by reducing the number of capsules from the open-label bottle (the active drug) by 1 for each dose level as indicated in Table 9. Additional PK assessments will be collected in all patients that have a dose reduction to enable exposure-response evaluation at the lower CORT125281 dose (Table 21).

Table 9 Dose Reductions of CORT125281 for Dose-Determination Phase Segment 2

Before Reductiona			First Dose Reductionb			Second Dose Reductionb		
	No. of Capsules from Each Bottle			No. of Capsules from Each Bottle			No. of Capsules from Each Bottle	
Dose Level	Open-Label	Blind-Label	CORT125281 Dose	Open-Label	Blind-Label	CORT125281 Dose	Open-Label	Blind-Label
+2	6 caps	2 caps	Prior dose – 40 mg	5 caps	2 caps	Prior dose – 40 mg	4 caps	2 caps
+1	6 caps	1 cap	Prior dose – 40 mg	5 caps	1 cap	Prior dose – 40 mg	4 caps	1 cap
1c	6 caps	0 cap	Prior dose – 40 mg	5 caps	0 cap	Prior dose – 40 mg	4 caps	0 cap

cap, capsule; No., number.
Note: The open-label bottle contains CORT125281 and blind-label bottle contains blinded capsules (CORT125281 [Arm A] or placebo [Arm B]).
a. Reduce CORT125281 by 40 mg according to the current dose level.
b. If a CORT125281 dose reduction is needed, the patient will have additional PK assessments (Table 21) after 14 days at the lower dose level to enable exposure-response evaluation at lower CORT125281 doses.

Once the dose has been modified for toxicity, re-escalation is not allowed.

If CORT125281 is discontinued, enzalutamide will be continued per the guidance provided in Section 5.7.1.1.

5.7.1.1 Continuation of Enzalutamide After CORT125281 Interruption/Discontinuation

The following guidelines apply for enzalutamide continuation in patients who discontinue CORT125281 or have a CORT125281 dosing interruption:

1. Patients may resume enzalutamide prior to resuming CORT125281 after the Investigator discusses with the Medical Monitor. The intent is for patients to maintain the dose intensity of enzalutamide per standard practice whenever possible.
2. For patients who have not progressed on enzalutamide or second-generation anti-androgen, if CORT125281 is discontinued, enzalutamide will be continued. Following the visit of the subsequent cycle (after discontinuing CORT125281), if all toxicities attributed to CORT125281 have resolved, study visits will occur at least every third cycle until discontinuation of enzalutamide (Section 7.3.1). Upon discontinuation of enzalutamide, the patient will return for the EOT and EOT +30 Days Visits.
3. Patients previously progressing on enzalutamide or second-generation anti-androgen will discontinue enzalutamide, if CORT125281 is discontinued.

Radiographic tumor assessments (CT/MRI, bone scan) should be continued until disease progression per the SoA (Table 16).

5.7.1.2 Monitoring for Excessive Glucocorticoid Receptor Blockade

Based on the mechanism of action of CORT125281, there is the possibility that patients could experience signs or symptoms related to excessive GR antagonism. If signs and/or symptoms of excessive GR antagonism such as malaise, fatigue, lethargy, weakness, anorexia, nausea, vomiting, abdominal pain, altered mental status, or hypoglycemia are present, particularly if co-existent, treatment with CORT125281 should be interrupted and the Medical Monitor should be consulted to assist in evaluating whether treatment should continue. Since CORT125281 does not block the mineralocorticoid receptor, it is unlikely that hypotension would be seen in the absence of anti-hypertensive medication. It is unlikely that hypoglycemia would be observed in the absence of glucose lowering medications.

If excessive GR antagonism is suspected, standard supportive care (including fluid resuscitation as indicated) and medical therapy should be administered without delay. Systemic administration of corticosteroids should be considered (eg, dexamethasone 4 mg daily for 3 days and then tapered by 1 mg per day, or as indicated based on clinical response). [redacted] In the event of significant trauma or surgery through 28 days after the final dose of CORT125281, supplemental GCs and appropriate medical care may be needed to prevent excessive GR antagonism that may arise due to increased cortisol requirements in the perioperative period.

5.7.2 Enzalutamide Dose Modification or Delay

If a patient experiences a Grade 3 or greater toxicity or an intolerable side effect, withhold enzalutamide and CORT125281 dosing for 1 week or until symptoms improve to Grade 1 or

less, or to the patient's baseline, then resume at the same or a reduced dose, if warranted. If a dose reduction of enzalutamide is required, the dose will be decreased by 40 mg for each reduction. A maximum of 2 dose level reductions of enzalutamide will be allowed. The maximum time a patient's study treatment may be held due to toxicity is 28 days; after which the patient must be discontinued from study participation. If enzalutamide is discontinued, CORT125281 will be discontinued.

5.8 Intra-Patient Dose Escalation

5.8.1 Intra-Patient Dose Escalation of CORT125281

5.8.1.1 Dose-Determination Phase Segment 1

Patients in this part of the study who have not experienced Grade 2 or greater toxicity attributed to CORT125281 may, upon discussion with the Medical Monitor, increase CORT125281 to a dose level that has been shown to be safe and well tolerated after studying data from later cohorts. PK will be collected per Table 20 to determine the impact of dose escalation on enzalutamide and CORT125281 exposures.

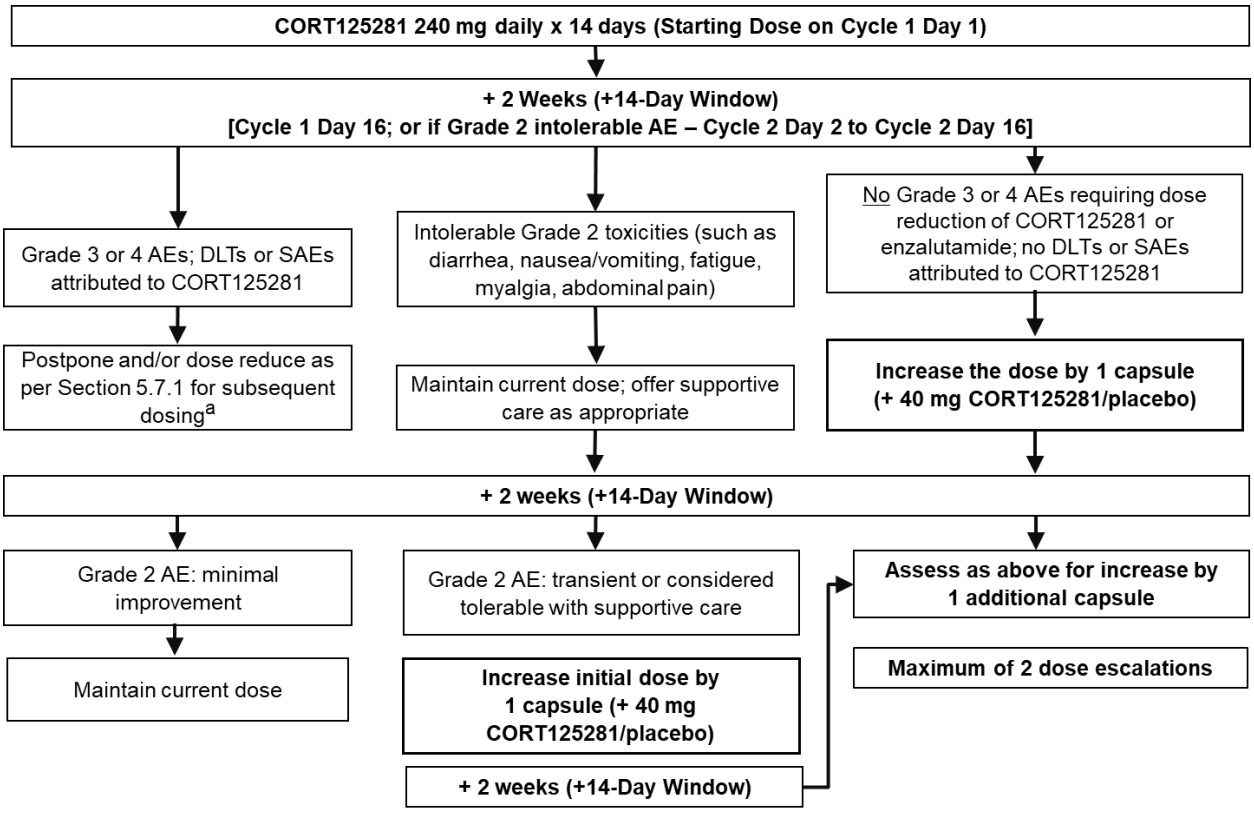
5.8.1.2 Dose-Determination Phase Segment 2

Patients in this part of the study will receive CORT125281 at a starting dose of 240 mg QD, with dose titration in 40-mg increments to a max dose of 320 mg QD (Arm A) or without an increase of the active dose (240 mg QD; Arm B). Patients in Arm B will receive placebo capsules, such that the patient, Investigators, and study team are blinded to the actual dose the patient is receiving.

All patients will start treatment with CORT125281 240 mg QD on Cycle 1 Day 1. Beginning on Cycle 1 Day 16, the dose will be escalated every 2 weeks, as tolerated, as shown in Figure 3. If any planned dose escalation is postponed due to a transient intolerable Grade 2 toxicity, the dose may be escalated within 14 days of the planned escalation.

After the DRC has determined the RD in Dose-Determination Phase Segment 2 (Section 5.4.2), patients assigned to Arm B who have not experienced dose reductions due to toxicity will then have their dose escalated in an open-label fashion per the RD regimen.

Figure 3 CORT125281 Intra-Patient Dose Escalation in Segment 2



[a.] Once the dose has been modified for toxicity, re-escalation is not allowed.

5.9 Prior and Concomitant Medications

The use of any prohibited, prior, or concomitant treatments will be recorded in the eCRF along with their daily dosage, duration, and reason for administration.

5.9.1 Permitted Concomitant Therapy Requiring Caution

The following medications are permitted but must be used with caution from 1 week before the first dose of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier) through the final treatment with enzalutamide:

- Moderate substrates of CYP2C9

This study allows for patients who discontinue CORT125281 to continue on enzalutamide alone (Section 5.7.1.1). The following restrictions only apply to patients on CORT125281 (ie, these medications will not be restricted in patients who are on enzalutamide alone).

Permitted medications to be used with caution from 1 week before Baseline through the final dose of CORT125281 are as follows:

- Moderate substrates of CYP2C8
- Warfarin: If co-administration of the study regimen with warfarin cannot be avoided, conduct additional INR monitoring.

- Sulfonylureas: For patients receiving sulfonylureas, conduct close glucose monitoring to assess for diabetic control.
- Corticosteroids:
  - Systemic corticosteroids. Short courses of prednisone for non–cancer-related reasons are permitted if clinically required. CORT125281 treatment should be withheld during corticosteroid administration, and the Medical Monitor should be notified.
  - Potent (Group III) topical corticosteroids should be used with caution due to the potential for systemic absorption, and the Medical Monitor should be contacted to discuss the treatment approach.

5.9.2 Prohibited Medications/Treatments/Foods

Anticancer agents including cytotoxic chemotherapy, hormonal therapy (other than LHRH analogues), immunotherapy, biologic therapy, therapeutic radiotherapy, or investigational agents are not permitted during the treatment portion of the study.

The following medications are prohibited from 1 week before the first dose of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier) through the last treatment with enzalutamide (for applicable wash-out periods, refer to Section 4.2):

- Strong inducers of CYP3A4
- Strong inhibitors or inducers of CYP2C8
- Sensitive substrates of CYP3A4
- Sensitive substrates of CYP2C9
- Sensitive substrates of CYP2C19

The following are prohibited from 1 week before Baseline through the final dose of CORT125281:

- Strong inhibitors of CYP3A4
- Treatment with systemic GCs or requirement for chronic or frequently used systemic GCs for medical conditions

Anticancer Chinese medicines or herbal remedies are not allowed. Herbal products or alternative therapies that may decrease PSA levels or that may have hormonal anti-prostate cancer activity (eg, saw palmetto, PC-SPES, PC-HOPE, St. John's wort, selenium supplements, grape seed extract) are not allowed. Other herbal products or vitamin supplements are not allowed for 14 days before the first dose of study treatment and until the last PK sample collection. Vitamins/supplements (such as potassium supplements for hypokalemia) will be allowed, if clinically indicated. These should be discussed with the Medical Monitor if their use is indicated during the PK-evaluation period.

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Grapefruit and/or Seville orange, including marmalade and juices made from these fruits from 14 days prior to the first dose of CORT125281 and/or enzalutamide and until the last treatment cycle is completed.

- Alcohol: Alcohol is known to induce CYP3A4 and may lead to reduced plasma exposure of enzalutamide. Alcohol use should be avoided from 48 hours before the first dose of study treatment and until the completion of intensive PK (Cycle 2 Day 1). Alcohol intake within the past 48 hours will be documented during study visits that include PK assessment.
- Note: Per the enzalutamide label, a high level of alcohol intake may predispose the patient to an increased risk of seizures. Thus, it is recommended that alcohol consumption be restricted to moderate intake in subsequent cycles (no more than 2 drinks per day; a standard drink is equivalent to 12 ounces [355 mL] of regular beer, 8 to 9 ounces [237 to 266 mL] of malt liquor [strong lager or ale], 5 ounces [148 mL] of wine, or 1.5 ounces [44 mL] of 80-proof distilled spirits).

Examples of medications, treatments, and foods that are prohibited or are to be used with caution are listed in Appendix C. It is not possible to produce an exhaustive list of medications that fall into the categories, so if in question, please refer to the appropriate product label. If the Investigator determines that such a medication is medically necessary, the Investigator will notify the Medical Monitor and discuss the Investigator's use of these medications and the Investigator's plans to medically monitor the patient. If co-administration with a strong CYP2C8 inhibitor or strong CYP3A4 inducer is necessary, the dose of enzalutamide will be adjusted per the locally approved product label.

5.9.3 Prior Medications

Patients will be excluded if they have taken or received any treatments listed in the exclusion criteria (see Section 4.2). Refer to Section 5.9.2 for additional restrictions on herbal products, vitamin remedies, or foods that may affect enzalutamide and/or CORT125281 exposures.

5.9.4 Concomitant Therapy

The locally approved product label, institutional guidelines, local practice, or applicable SmPC for enzalutamide should be referenced for any concomitant therapy guidelines.

Best supportive care and treatment will be given as appropriate to each patient (antiemetics, antibiotics, transfusions, nutritional support, non-radiation palliative treatment for pain, bisphosphonates, or denosumab) according to institutional guidelines or American Society of Clinical Oncology guidelines.

If the patient requires surgery or palliative radiotherapy during the study, then this needs to be discussed with the Medical Monitor.

5.10 Meals and Dietary Requirements

For all fasting laboratory tests (eg, blood hormones), patients should not take food or beverage, except water to quench thirst, from 8 hours prior to dosing until after collection of the sample. The fasting status will be recorded in the appropriate eCRF by the Investigator (or designee).

5.10.1 Dose-Determination Phase Segment 2

Patients in this part of the study will take their CORT125281 with their evening meal, unless otherwise specified (eg, for PK/PD assessments). If the patient is unable to eat prior to their scheduled dose, they should proceed with administering their daily dose rather than omitting it.

5.10.2 Expansion Phase

Food-Effect Subcohort:

- Fasting: On Cycle 1 Day -7, patients will not be allowed to take food or beverage, except water to quench their thirst, from 8 hours prior to dosing until after collection of the 4-hour blood sample. No fluids except those required for dosing will be allowed for 1 hour before dosing and 1 hour after dosing.

Standard Breakfast: On Cycle 1 Day 1, a standard breakfast (Appendix D) will be provided at the study site prior to administration of CORT125281. The meal will consist of approximately 520 Kcal; with approximately 30% calories from fat.

5.11 Method of Treatment Assignment and Randomization

5.11.1 Dose-Determination Phase Segment 1 and Expansion Phase

Dose-Determination Phase Segment 1 and the Expansion Phase are open label. No randomization or allocation methods will be used in these parts of the study.

5.11.2 Dose-Determination Phase Segment 2

All patients enrolled in Dose-Determination Phase Segment 2 will be centrally assigned to randomized study treatment using interactive response technology (IRT). Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

Once Screening procedures are complete eligible patients will be randomized in a 3:1 ratio to Arm A (enzalutamide + titrated dose of CORT125281 [240 mg to 320 mg]) and Arm B (enzalutamide + CORT125281 240 mg).

5.12 Blinding

5.12.1 Dose-Determination Phase Segment 1 and Expansion Phase

The Phase 1 Segment 1 and Phase 2a parts of the study are open label. No blinded study treatments will be used in these parts of the study.

5.12.2 Dose-Determination Phase Segment 2

The Phase 1 Segment 2 part of the study is double blinded for dose titration with respect to CORT125281 in combination with enzalutamide. All patients will receive CORT125281 at a minimum starting dose of 240 mg QD. Approximately 20 patients will be enrolled to achieve 16 DLT-evaluable patients randomized. Randomization will be conducted by IRT in a 3:1 ratio to receive CORT125281 in combination with enzalutamide either with the starting dose of CORT125281 240 mg with dose- titration to 320 mg QD (N=12; Arm A) or with the starting

dose of CORT125281 240 mg, without titration of the dose (N=4; Arm B). Dose titration of CORT125281 in Arm B will occur with placebo, such that the patient, Investigators, and study teams are blinded to which patients are receiving (ie, 240 mg versus 240 mg to 320 mg). During this part of the study, an unblinded Medical Monitor independent of the study team will provide additional oversight for the study, including review of serious unexpected AEs considered related to either CORT125281 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 (Section 9.8). Once the DRC has determined the RD, patients assigned to Arm B who have not experienced any dose reductions due to toxicity will then have their dose escalated in an open-label fashion per the recommended upward titration regimen.

5.12.2.1 Unblinding

The Sponsor or designee, the Investigator, the blinded Medical Monitor, study-site personnel, and the patient will be blinded to treatment assignment in Dose-Determination Phase Segment 2. After all patients complete 3 cycles of treatment or discontinue treatment, the data will be unblinded and the DRC will meet to review available data.

The IRT system will include a mechanism to permit rapid unblinding in emergency situations, if the Investigator considers it in the best interest of the patient. To maintain the overall quality and legitimacy of the clinical trial, unblinding should only occur in exceptional circumstances. If unblinding is deemed necessary, the Investigator should complete the unblinding process through the IRT system. If the IRT system is unavailable, the Suvoda Help Desk may be contacted to serve as a backup system to enable unblinding of the treatment assignment. Information on unblinding procedures and the Suvoda Help Desk contacts can be found in the IRT Site User Manual.

Investigators wishing to discuss potential unblinding occurrences should contact the Medical Monitor for further discussion. The Investigator should promptly notify the Sponsor of any unblinding occurrences.

If unblinding of central laboratory data is required, the site should refer to the Central Laboratory Manual for the unblinding process. Note: Even if laboratory values are unblinded, the treatment assignment will remain blinded.

The Investigator is encouraged to maintain the blind as far as possible. The patient's treatment assignment must not be disclosed to the patient and/or other study staff. There should not be any written or verbal statements of the patient's treatment assignment in any patient documents.

If any accidental unblinding occurs, the Investigator should promptly document the occurrence and immediately notify the Sponsor (on the same day if possible).

5.13 Patient Diary Card

Patient diary cards will be dispensed to the patient at Day 1 of each cycle. Patients will be instructed to return all unused study drug and the dose diary during each patient visit. Patients should complete an entry in the diary for each self-administered dose of CORT125281 and enzalutamide. Entries will include the number of capsules as well as the date and time of

CORT125281 and enzalutamide administration. On visit days, CORT125281 and enzalutamide should be taken in the clinic during the visit and after initial blood draws. The date and time of the previous dose and the time and dose administered in the clinic should be documented in the clinic charts.

5.14 Product Accountability and Treatment Adherence

Patients will be instructed to return all used and unused study drug containers at each study visit. Patient compliance with the dosing regimen will be assessed on Day 1 of each cycle and at the EOT Visit by reconciliation of the used and unused study drug. The quantity dispensed, returned, used, or lost must be recorded at these visits. Procedures for return and disposition of study drug by the clinical site are provided in Section 11.5.

6 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES AND APPROPRIATENESS OF MEASUREMENTS

Study procedures and their timing are summarized in Appendix A, SoA. Protocol waivers or exemptions are not allowed.

The Investigator and Sponsor will conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct, and the Investigator must ensure that trial procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in the SoA.

6.1 Informed Consent and Screening

Written informed consent must be obtained in order for a patient to participate in this study. The informed consent form (ICF), which has been approved by the appropriate IRB/IEC, must be signed by the patient before any protocol-directed procedures are performed. The ICF must also be signed before any prohibited medications are withheld from patient in order for the patient to participate in the study.

Study patients must be notified of any changes that might affect their willingness to continue in the study in an update to the ICF and be given the opportunity to ask questions and/or withdraw consent. The patient's agreement must be documented in writing.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Appendix A).

6.2 Medical and Oncology History

The following information will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use
- Presence and severity of any symptoms/conditions associated with metastatic prostate cancer
- Presence or absence of bone metastases on bone scan and lesion number described in Appendix B
- Detailed oncology history, including but not limited to:
  - Date of primary cancer diagnosis
  - Pathology (histology or cytology) of primary tumor
  - Surgical history
  - Anticancer and radiation treatments administered (including dates, type of modality, response, and reason for discontinuation)
  - Metastasis information (including the location and histological markers), if applicable

- Prior molecular testing/tumor profiling (including repeat biopsy from primary pathology, blood-based assays for molecular markers, and determinants of prognosis or drug sensitivity). The data collected will be the results of tumor molecular profiling or genetic testing relevant to prostate cancer and may include testing for defects in homologous recombination (such as BReast CAncer genes 1 or 2 [BRCA1 or BRCA2] mutation), AR mutation testing, and molecular profiling.
- Any new or clinically significant changes in the patient's medical or oncologic history between signing of the IRB/IEC-approved ICF and the first dose of study treatment will be recorded on the AE eCRF page

6.3 Safety Measures

Safety will be determined by evaluating study drug exposure, AEs, serious adverse events (SAEs), all deaths, changes in laboratory determinations, and vital sign parameters. Vital signs, laboratory tests, and performance status assessment will be performed prior to dosing on the visit days where the first dose of CORT125281 is taken, the first dose of enzalutamide is taken, and Cycle 1 Day 1 for all patients.

6.3.1 Physical Examination

Complete physical examinations and limited physical examinations will be performed at the time points noted in the SoA (Appendix A). At each visit after the first dose of CORT125281 and/or enzalutamide, the Investigator will perform an assessment focused on determining if the patient's disease has progressed, based on the standard of care at each site. The performance of the physical exam will be recorded in the appropriate eCRF by the Investigator (or designee).

Limited physical examinations will include assessment of skin, heart, lungs, and abdomen, in addition to symptom-directed assessment of other organ systems. Note: all clinically significant abnormalities occurring before signature of informed consent should be recorded in the Medical History and/or Oncology History section of the eCRF; all abnormalities occurring or worsening after signature of informed consent should be recorded in the AE section of the eCRF.

Weight will be reported at each visit where a physical examination is performed. Height will be recorded at Screening only. Height and weight (without shoes) will be measured using an appropriate measuring device. Historical patient information and/or patient reports should not be used for either measurement.

6.3.2 Vital Signs

Vital signs (blood pressure, heart rate, respiration rate, temperature) will be assessed at the time points shown in the SoA (Appendix A).

Systolic and diastolic blood pressure and heart rate will be measured after patients have been at rest (seated) for at least 3 minutes. If possible, blood pressure and heart rate measurements should not take place immediately after scheduled blood collections.

6.3.3 ECOG Performance Status

ECOG performance status (Table 10) will be assessed at Screening, at each study visit; at the EOT Visit, and at the EOT +30 Days Visit.

Table 10 ECOG Performance Status

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

ECOG, Eastern Cooperative Oncology Group.
Source: Oken et al. 1982

6.3.4 12-Lead Electrocardiogram

12-lead ECGs will be obtained in triplicate (3 recordings made at intervals of at least 2 minutes apart) at Screening; at Cycle 1 Day 1 (before dosing and 2 hours post-dose ±10 minutes), Cycle 1 Day 15 (before dosing and 2 hours post-dose ±10 minutes), Cycle 3 Day 1 (before dosing and 2 hours post-dose ±10 minutes); and at the EOT +30 Days Visit. The Investigator or Sub-Investigator (physician) will be responsible for review and interpretation of the ECG results and determining whether the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. The ECG tracing with the physician's interpretation should be initialed, dated, and retained in the patient's records at the study site.

6.3.5 Adverse Events

Details on definitions and reporting of AEs are provided in Section 8.

All AEs will be recorded from the time of signing of the ICF until 30 days after the final dose of study treatment (CORT125281 or enzalutamide, whichever is later).

6.3.6 Clinical Laboratory Assessments

6.3.6.1 Laboratory Parameters

Clinical laboratory tests for safety and PD are listed in Table 11 and will be performed at the time points shown in the SoAs (Appendix A). Sample collections for PK are described in Section 6.6.

Safety laboratory samples will be analyzed at local laboratories, cortisol and ACTH tests may be performed locally to fulfill the eligibility criteria requirements. Other laboratory procedures will be analyzed as described in the Central Laboratory Manual.

Any abnormal test results determined to be clinically significant by the Investigator should be repeated within no more than 1 week until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant. If it is not feasible to repeat testing, the reason will be documented. All abnormal clinical laboratory result pages should be initialed and dated by an Investigator, along with a comment regarding whether or not the result is clinically significant.

In the event of an SAE, DLT, or significant change in clinical status, ACTH and cortisol should be assessed; and a PK sample may be drawn at the discretion of the Investigator.

The Investigator will review all laboratory reports, evaluate the results, and sign/date the report.

Patients will be in a seated or supine position during blood collection.

Table 11 List of Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cell (RBC) count	Sodium	Bacteria
Hemoglobin	Potassium	Blood
Hematocrit	Calcium	Urobilinogen
Mean corpuscular volume (MCV)	Chloride	Nitrites
Platelet count	Phosphorus	Color
White blood cell (WBC) count	Magnesium	Clarity
WBC with 5-part differential:	Serum Creatinine	pH
Neutrophils	Total bilirubin	Specific gravity
Lymphocytes	Albumin	Ketones
Monocytes	Alkaline phosphatase (ALP)	Protein
Eosinophils	Lactic dehydrogenase (LDH)	Glucose
Basophils	Aspartate aminotransferase (AST)	Bilirubin
Coagulation	Alanine aminotransferase (ALT)	Leukocyte esterase
Prothrombin time (PT)	Glucose, document if fasting or non-fasting	**Pharmacodynamic [a]**
Activated partial thromboplastin time (aPTT)	Blood urea nitrogen (BUN)	ACTH
International normalized ratio (INR)	Uric acid	Cortisol
Other	Bicarbonate	DHEA-S
Pharmacogenomic sample [b]	Total protein	Androstenedione
Hepatitis B and C serologies [c,d]	**Thyroid Function**	Estradiol
HIV immunoassay [c,e]	Thyroid-stimulating hormone (TSH)	Testosterone, total and free
Prostate-specific antigen (PSA)	Free thyroxine (FT4) [f]	UFC (with creatinine)
Serum amylase	Total triiodothyronine (T3) [f] or	Spot urine (with creatinine)
Serum lipase	Free triiodothyronine (FT3) [f]	

ACTH, adrenocortical hormone; DHEA-S, dehydroepiandrosterone-sulfate; HIV, human immunodeficiency virus; UFC, urinary free cortisol.

Note: Sample collections for pharmacokinetics are described in Section 6.6.

a. Pharmacodynamic samples are to be drawn as described in the Schedule of Pharmacodynamic Assessments (Table 17 [Dose-Determination Phase Segment 1], Table 18 [Dose-Determination Phase Segment 2], and Table 19 [Expansion Phase]).

b. For patients in Dose-Determination Phase Segment 1 only.

c. Must be confirmed as negative prior to enrollment.

d. Serologic assays for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), and anti-hepatitis C antibodies.

e. Fourth generation immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen.

f. Reflex testing only with abnormal TSH values.

6.3.6.2 Sample Collection, Preparation, and Shipping

Complete instructions for collection, preparation, and shipping of all laboratory samples will be provided by the central laboratory/laboratories in the Central Laboratory Manual. Shipping instructions for samples collected for PK analysis, will also be provided.

6.4 Pharmacodynamic Measures

The development and improvement of cancer therapies increasingly depends on insights gained from analysis of biomolecules. During this study and with the consent of patients, biological samples (eg, blood, plasma, serum, or tumor tissue) will be obtained, some for analysis during the study and others for future analysis. These samples will be used to develop a better understanding of the mechanisms of both treatment response (predictive biomarkers) and disease processes (prognostic biomarkers) and ultimately to identify which patients have a high probability to benefit from treatment with CORT125281 in combination with enzalutamide and which do not. If tumor tissue, CTCs, and plasma are available from the same patient, the results of studies will be compared to assess correlation of the methodologies.

Candidate biomarkers that will be investigated during the study include the following:

- Tumor expression of GR via IHC
- Assay of mRNA expression of GC-modulated pathways in whole blood and tumor
- CTCs: enumeration, GR expression, ARV7, and exploratory biomarkers
- Plasma ACTH, serum cortisol, 24-hour UFC (and creatinine), and spot urine test for cortisol (and creatinine) to assess modulation of the HPA axis
- Dehydroepiandrosterone-sulfate, androstenedione, testosterone (free and total) and estradiol levels
- Whole blood for circulating tumor DNA and exploratory biomarkers (such as circulating ARV7 transcripts or exosome RNA), based upon the most accepted methodology at the time of the analysis)
- Neutrophil-to-lymphocyte ratio and relative abundance of other cells in the blood (from the complete blood count)

The tests will be conducted at the central laboratory/laboratories using a variety of techniques (eg, IHC, DNA/RNA analysis). PD assays may be performed to correlate results of biomarker assessments to the physiological effects of CORT125281. Refer to the PD SoAs (Table 17 [Dose-Determination Phase Segment 1], Table 18 [Dose-Determination Phase Segment 2], and Table 19 [Expansion Phase]) for the timing and frequency of all sample collections.

For all fasting samples (obtained between 7 and 9 a.m., unless otherwise specified), patients will not be allowed to take food or beverage, except water to quench their thirst, from 8 hours prior to sample collection until after the sample collection. See the Central Laboratory Manual for details of preparation, storage, and shipping of PD samples.

6.4.1 Blood Hormones for HPA Axis Effects

Modest elevations in cortisol were observed after high doses of CORT125281 in a Phase 1 healthy volunteer study (Study CORT125281-600). While these elevations were not clinically

significant, assessing cortisol in blood and urine (see Section 6.4.5) may aid in the identification of an optimal dose of CORT125281 in this study.

6.4.2 Blood for mRNA Analysis of GC-Related Pathways and Exploratory Biomarkers

A broad array of transcriptional programs is controlled by GR. Transcription of GR-related genes will be assessed in whole blood to determine the biological activity of CORT125281 and to aid in the identification of an optimal dose of CORT125281 in this study.

6.4.3 Circulating Tumor Cells

In prostate cancer patients, rare tumor cells can be found and isolated in circulation. The frequency of these cells will be assessed. Further, the cells will be probed for GR expression and the presence of an AR variant called ARV7. These data may provide insight into the biological activity of CORT125281 and mechanisms of resistance to AR and/or GR targeted therapy.

6.4.4 Paired Tumor Tissue Biopsies

Paired tumor biopsies will be collected for determination of GR status and exploratory biomarkers.

The baseline biopsy should be obtained within 6 weeks prior to initiating study treatment (CORT125281 or on-study enzalutamide, whichever is earlier). Soft tissue biopsy is preferred, when possible. An additional paired biopsy will be collected at Cycle 2 Day 1 (window of within 14 days prior to Cycle 2 Day 1 is acceptable). It is preferred that this biopsy be collected from the same lesion as the baseline sample, if sufficient tissue remains and if logistically feasible.

For a subset of patients, consent to provide paired tissue biopsies may be mandatory to meet a minimum number of samples per cohort, as below. In the remainder of patients, the paired tumor biopsies will be optional. The requirement for biopsies will be communicated to each patient during the enrollment process.

- Dose-Determination Phase Segment 1: A sufficient number of patients will be enrolled to provide paired biopsies in approximately 4 patients per cohort.
- Dose-Determination Phase Segment 2: A sufficient number of patients will be enrolled to provide paired biopsies in approximately 10 patients (total).
- Expansion Phase: A sufficient number of patients will be enrolled to provide paired biopsies in approximately 10 patients per cohort.

Optional biopsies may also be collected during standard-of-care procedures or at the time of disease progression with consent of the patient. Refer to the Central Laboratory Manual for complete instructions on sample collection and handling.

For patients whom paired biopsies are considered mandatory, patients must have at least 1 lesion accessible that is safely accessible for biopsy at each time point to be eligible for enrollment. Tissue acquisition, with or without anesthesia, must be considered of low risk to the patient. Biopsy of lesions that pose an undue risk to the patient, such as mediastinal lymph nodes, will not be performed as part of this study. In the case where biopsy samples are unable to be obtained for a given patient, the patient will remain on study, receive study treatment and all

study procedures will be performed. Please contact the Medical Monitor if any of the specimens are not feasible to collect.

GR expression will be assessed by IHC by a central laboratory. The results will be reported as the percentage of tumor cells with nuclear staining at different intensities, total percentage cells with nuclear staining (P-score), and as H-score. Tissue may be used to assess molecular characteristics and/or expression of protein, nucleic acids, and metabolites. Microarray analysis of tumor-derived RNA may include and GC-induced genes or biomarkers of GR activity. Analyses of relevant proteins, including IHC for GR, will be performed on paired tumor tissue specimens, when feasible.

6.4.5 Urinary Free Cortisol and Urine Spot Test

During Dose-Determination Phase Segment 2 and the Expansion Phase, each patient will be provided with instructions and supplies to collect all urine produced during a 24-hour period. The 24-hour urine creatinine level and total 24-hour urine volume will be obtained to confirm complete collection of the urine. The patient should avoid drinking an unusual amount of fluids (≥5 L/day) during the 24-hour period. Patients should avoid use of any GC preparations, including steroid-containing skin or hemorrhoid creams, during the collection period. For the 24-hour UFC collection, the patient is instructed to void the first urination of the day and then collect all subsequent urinations for a 24-hour period. The 24-hour UFC will include the first morning urination on the following day.

The patient should bring the urine to the visit, as specified in the PD SoA (Table 18 [Dose-Determination Phase Segment 2] and Table 19 [Expansion Phase]). UFC and creatinine will be measured by tandem mass spectrometry.

At the visits following 24-hour UFC collections, a spot urine sample will also be collected to assess cortisol and creatinine. This can occur at any time of the day. This cannot include urine from the first morning urination on the day of the visit, as that needs to be part of the 24-hour urine collection for UFC.

6.5 Pharmacogenomic Testing

During Dose-Determination Phase Segment 1 only, a blood sample will be collected at baseline to assess genetic factors involved in the metabolism, safety, and efficacy of CORT125281 and enzalutamide. If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit.

6.6 Pharmacokinetic Measures

The plasma concentration data for CORT125281, CORT125324 (metabolite of CORT125281; Ki >10 μM at the GR), enzalutamide, M2, and enzalutamide carboxylic acid (inactive metabolite of enzalutamide) will be analyzed using non-compartmental methods to obtain estimates of standard PK parameters.

- Dose-Determination Phase Segment 1

  - Lead-in Period: Plasma samples will be collected over a 24-hour period on the day prior to initiating CORT125281 to determine the PK parameters of enzalutamide and major metabolites.
  - Combination Treatment Period: Plasma samples will be collected to assess the PK profile of CORT125281, enzalutamide, and their major metabolites to determine steady-state CORT125281 PK parameters and to assess the effect of CORT125281 on exposure to enzalutamide.
    - Cycle 1 Day 1
    - Cycle 1 Day 22 (partial profile)
    - Cycle 2 Day 1
    - Cycle 2 Day 15 and Cycle 3 Day 1 (partial profile)
- Dose-Determination Phase Segment 2
  - Combination Treatment Period: Plasma samples will be collected to assess PK parameters of CORT125281 and enzalutamide.
    - Cycle 1 Day 15
    - Day before second dose escalation (eg, Cycle 2 Day 1 or Cycle 2 Day 15)
- Expansion Phase:
  - Food-Effect Subcohort (10 patients in the Abi-Resistant Cohort):
    - Cycle 1 Day -7 and Day 1: Plasma samples will be collected to determine CORT125281 PK parameters
  - All patients in the Expansion Phase: Plasma samples to be collected on Cycle 2 Day 1 and Cycle 3 Day 1 to determine the concentration of CORT125281, enzalutamide, and their major metabolites.

Refer to the SoAs in Table 20 (Dose-Determination Phase Segment 1), Table 21 (Dose-Determination Phase Segment 2), and Table 22 (Expansion Phase) for the timing and frequency of all PK sample collections.

6.7 Exploratory Measures of Anticancer Activity

Response to treatment will be determined using PCWG3 recommendations (Eisenhauer et al. 2009; Scher 2016; Appendix B).

Radiologic tumor assessments: CT of the chest, abdomen, and pelvis, and ^{99}mTc-methylene radionucleotide bone scintigraphy should be performed within 28 days prior to the first dose of enzalutamide (for Dose-Determination Phase Segment 1) and/or CORT125281 (for Dose-Determination Phase Segment 2 and the Expansion Phase). CT scan with ≤5-mm axial slices is advised for all patients. A cross-sectional magnetic resonance imaging (MRI) scan of the abdomen and pelvis, with a non-contrast CT scan of the chest is acceptable for patients who are intolerant of contrast. To ensure comparability, the baseline radiographs/scan, and subsequent radiographs/scans to assess response, should be performed using consistent methods and identical techniques. The same method (radiological or physical) should be employed and assessed by the same individual on each occasion, if possible. Radiographic tumor assessments should be performed every 8 weeks from the first dose of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier) for the first 24 weeks and every 12 weeks thereafter, at

the EOT Visit (if not performed within 4 weeks), and as clinically indicated. For on-study scans, a window of ±14 days is acceptable with the timing of the scans based on Cycle 1 Day 1. The rPFS per PCWG3 will be assessed.

Blood-based markers: PSA, ALP, and LDH will be assessed during the Baseline/Screening Visit, Day 1 of each cycle, and EOT Visit. Results will be documented in the eCRF.

Survival: Patients will be followed for survival every 4 months until 2 years from the date that the last patient enrolls in the study.

6.8 Concomitant Medication Assessments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at Screening, receives during the study, and up to 30 days following the final dose of study treatment must be recorded in source documents and the eCRFs. The reason for use, dates of administration (including start and end dates), and dosage information (including dose and frequency) must be recorded.

6.9 Patient-Reported Outcomes and Quality-of-Life Assessments

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and additional questions to capture patient-reported pain will be used on study.

The FACT-P questionnaire is a validated questionnaire, used worldwide for assessing the health-related QoL in men with prostate cancer. FACT-P consists of FACT-G (general), a 27-item self-report questionnaire that measures general health-related QoL in cancer patients, and a 12-item prostate cancer subscale (PCS). The PCS is designed specifically to measure prostate cancer-specific QoL. Patients' overall physical and emotional well-being, based on subscales of the FACT-G and the PCS, PCS pain-related score, and other prostate cancer-specific QoL components, will be assessed using the questionnaire.

Questions to capture the patients reported pain will be reported in the appropriate eCRFs in addition to the FACT-P questionnaire. Pain is the most established PRO in the mCRPC population and is associated with inferior survival and diminished QoL (Scher et al. 2016).

The PRO and QoL questionnaires will be completed at the time points shown in the SoA (Appendix A). The questionnaires should be administered before discussing imaging scan results or disease status changes with the patient. The questionnaires should continue as a study procedure in patients who discontinue study treatment prior to disease progression until unequivocal progressive disease is documented. The questionnaires can be administered by self-report (paper) or interview by qualified site personnel (face-to-face or telephone).

The Sponsor will provide training for relevant personnel (eg, key Investigators, clinical research associates) in the administration of the questionnaires, so that patients fill in the questionnaires as completely and accurately as possible. It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection. The measures are self-reported and the patient must complete the questionnaires in private and should not be given help from relatives or clinic staff; help in interpreting the questions is not allowed.

6.10 Appropriateness of the Measures

Standard clinical, PK, statistical, and laboratory procedures will be utilized in this study. The efficacy measurements in this study are standard.

7 STUDY ASSESSMENTS AND PROCEDURES BY STUDY VISIT

Schedules of assessments are provided in Appendix A.

7.1 Screening Period

Screening will be within 28 days before the first dose and may take place on more than 1 day within the 4-week Screening Period. If a patient was screened more than 4 weeks before the date of their first administration of study treatment (eg, if the study is delayed or the patient was initially screened as a standby patient for an earlier cohort), that patient must be re-screened. A patient who has failed Screening due to a reason that is temporary and expected to resolve (eg, mild intercurrent infection) may be re-screened.

At the start of Screening, the study will be discussed with the patient, and a patient wishing to participate must give written informed consent prior to any study-related procedures or change in treatment. The patient must also give written authorization regarding privacy requirements prior to any study-related procedures or change in treatment.

After written informed consent is obtained, prospective patients will be evaluated for entry into the study according to the inclusion and exclusion criteria (Sections 4.1 and 4.2). Each patient who receives study treatment will be assigned a patient number that will be used on patient documentation throughout the study.

The following Screening procedures will be performed:

- Record medical/oncologic history
- Record prior medications
- Complete physical examination
- Measure height
- Measure body weight
- Vital signs
- ECOG performance status
- 12-lead ECGs (performed in triplicate)
- Local laboratory tests (see Table 11 for details)
  - Complete blood count (CBC) with differential
  - Chemistry, including amylase, lipase, and LDH
  - Prothrombin time (PT), aPTT, and INR
  - Urinalysis
  - Thyroid-stimulating hormone (TSH), with reflex free thyroxine (FT4) and free or total triiodothyronine (FT3 or TT3)
  - Hepatitis B and C serologies and HIV immunoassay
- PD sampling (see Table 17 [Dose-Determination Phase Segment 1], Table 18, [Dose-Determination Phase Segment 2], and Table 19 [Expansion Phase] for details)
- Pharmacogenomics sampling (Dose-Determination Phase Segment 1 only)
- Tumor assessment:
  - Chest, abdomen, and pelvis CT scan with contrast
  - PSA

  - Tumor assessment documented per PCWG3
- Archival tumor tissue collection or on-study tumor biopsy

7.2 Lead-In Period (for Patients in Dose-Determination Phase Segment 1 and Patients in the Expansion Phase Food-Effect Subcohort Only)

During the Lead-In Period, patients will be treated with enzalutamide monotherapy (Dose-Determination Phase Segment 1) or CORT125281 monotherapy (Expansion Phase, Food-Effect Subcohort only). The lead-in duration is 28 days for patients in Dose-Determination Phase Segment 1, and 7 days for patients in the Expansion Phase Food-Effect Subcohort. When an RD of enzalutamide is determined by the DRC, the DRC may recommend discontinuing the lead-in for subsequent cohorts.

The first in-clinic visits will occur in the morning on the following days:

- Cycle 1 Day -28 for patients enrolled in Dose-Determination Phase Segment 1
- Cycle 1 Day -7 for patients enrolled in the Expansion Phase Food-Effect Subcohort

Study-related activities to be performed at the in-clinic visits are described in Appendix A.

Study treatment and patient diary cards will be dispensed as described in Section 5 and Section 5.13, respectively, and the following should be performed:

- Instruct the patient to take enzalutamide as per Table 3 (Dose-Determination Phase Segment 1) or CORT125281 as per Table 5 (Expansion Phase Food-Effect Subcohort).
- Have the patient take the first dose of study treatment and enter the information into the patient diary card.
- Review the dosing instructions for the study treatment with the patient, answer any questions, and remind the patient to bring the unused study treatment to the next visit.

Only patients in Dose-Determination Phase Segment 1 will receive enzalutamide monotherapy during the Lead-In Period. These patients will return on Cycle 1 Day -1 for enzalutamide PK sampling. PK assessments will be performed as described in Appendix A.

7.3 Combination Treatment Period

Cycle 1 will begin the day after Screening is complete for patients in Dose-Determination Phase Segment 2 and the following patients in the Expansion Phase:

- Patients in the Abi-Resistant Cohort who are NOT in the Food-Effect Subcohort
- All patients in the ARant-Resistant Cohort

Cycle 1 will begin the day after the Lead-In Period is complete for all patients in Dose-Determination Phase Segment 1 and patients in the Expansion Phase Food-Effect Subcohort.

The acceptable visit window is ±1 day for all visits during Cycle 1, unless the window spans a weekend; and ±3 days for all other cycles. Visit windows are relative to Cycle 1 Day 1.

Study-related activities to be performed at the in-clinic visits are described in Appendix A.

The following assessments should be performed during each in-clinic visit during the Combination Treatment Period:

- Record concomitant medications
- Record AEs
- Physical examination
- Vital signs
- ECOG performance status
- Local laboratory tests (see Table 11 for details)
  - CBC with differential
  - Chemistry, including LDH
- Review diary card

The following assessments should be performed on Day 1 of each cycle:

- Measure body weight
- Triplicate 12-lead ECG (Day 1 of Cycle 1 and Cycle 3 only, and Day 15 of Cycle 1)
- Local laboratory tests (see Table 11 for details)
  - PT, aPTT, and INR (Day 1 of Cycles 1 through 3)
  - Urinalysis (Day 1 of Cycles 1 through 3 and every third cycle after Cycle 3)
  - TSH, with reflex FT4 and TT3 or FT3 (every 3 months for the first year, starting with Day 1 of Cycle 3, and then every 6 months after the first year)
  - PSA
  - Serum amylase and lipase (each study visit through completion of Cycle 3, then every 3 months until completion of 12 months of study treatment)
- Dispense study treatment
- Provide patient diary card
- Study treatment accountability

Following the baseline/pre-treatment assessment, radiographic tumor assessments should be performed 8 weeks from the first dose of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier), and then every 8 weeks for the first 24 weeks and every 12 weeks thereafter. For on-study scans, a window of ±14 days is acceptable with the timing of the scans based on Cycle 1 Day1.

The PRO and QoL questionnaires should be completed prior to the first dose of study treatment (CORT125281 and/or enzalutamide); on Cycle 1 Day -28 or Cycle 1 Day -7 for patients in the Lead-In Period; Cycle 1 Day 1 for patients with no Lead-In Period; at the completion of the Lead-In Period for patients in the Lead-In Period (Cycle 1 Day 1); Cycle 3 Day 1; every 3 cycles after Cycle 3 Day 1; and at the EOT Visit.

In the event of an SAE, DLT, or significant change in clinical status, ACTH and cortisol should be assessed; and a PK sample may be drawn at the discretion of the Investigator.

A biopsy sample will be collected at Cycle 2 Day 1 (window of within 2 weeks prior to Cycle 2 Day 1 is acceptable) (Section 6.4.4). It is preferred that this biopsy be collected from the same lesion as the baseline sample, if sufficient tissue remains and if logistically feasible.

PD sampling will occur as described in Table 17 (Dose-Determination Phase Segment 1), Table 18 (Dose-Determination Phase Segment 2), and Table 19 (Expansion Phase).

PK sampling will occur as described in Table 20 (Dose-Determination Phase Segment 1), Table 21 (Dose-Determination Phase Segment 2), and Table 22 (Expansion Phase).

7.3.1 Discontinuation of CORT125281 (and Continuation of Enzalutamide Alone)

Upon discontinuation of CORT125281, the patient should have PD samples collected within 7 days of their final CORT125281 dose (Table 17-Table 19).

If the patient continues on enzalutamide alone (Section 5.7.1.1), visit frequency can be decreased per the Investigator's standard of care. The patient should come for their regularly scheduled visit for the subsequent cycle after discontinuing CORT125281. After this visit, if all toxicities attributed to CORT125281 have resolved, visits can be conducted less frequently per the Investigator's discretion, but at a minimum every 3 cycles while on enzalutamide alone. At study visits while on enzalutamide alone, patients will have the following assessments:

- Record concomitant medications
- Record AEs
- Physical examination
- Measure body weight
- Vital signs
- ECOG performance status
- Local laboratory tests
  - CBC with differential
  - Chemistry, including LDH
  - PSA
- Dispense study treatment
- Provide patient diary card
- Study treatment accountability

Radiographic tumor assessments (CT/MRI, bone scan) should be continued until disease progression per the SoA (Table 16). Upon discontinuation of enzalutamide, the patient should return for the EOT and EOT +30 Days Visits.

7.3.2 Cycle 1 Day 2

On Cycle 1 Day 2, patients in the Expansion Phase Food-Effect Subcohort will self-administer the first dose of enzalutamide at home.

7.4 End-of-Treatment Visit

Upon discontinuation of both study treatments (CORT125281 and enzalutamide), the patient should return to the clinic for an EOT Visit. The following assessments should be performed during the EOT Visit:

- Record concomitant medications
- Record AEs
- Physical examination
- Measure body weight

- Vital signs
- ECOG performance status
- Local laboratory tests (see Table 11 for details)
  - CBC with differential
  - Chemistry, including LDH
  - Urinalysis
- Tumor assessment, if not completed within 4 weeks
- PSA
- PD sampling (see Table 17 [Dose-Determination Phase Segment 1], Table 18 [Dose-Determination Phase Segment 2], and Table 19 [Expansion Phase] for details)
- Study treatment accountability

If study treatment is discontinued during a regular study visit, the regular visit will become the EOT Visit. Any additional procedures that would not be performed for the regular study visit should be performed for the EOT Visit.

7.5 Post-Treatment Follow-Up Period

If the patient discontinued CORT125281 and enzalutamide for reasons other than disease progression, tumor assessments will be collected and documented until disease progression.

All patients will continue to be followed until the study endpoints are met (radiographic disease progression, SSE, and overall survival). Phone follow-up for overall survival (ie, the date and cause of death, and post-treatment information) will continue every 4 months until 2 years from the date that the last patient enrolls in the study or until all patients have completed follow-up for radiographic disease progression (whichever is later).

7.5.1 End-of-Treatment +30 Days Visit

The following assessments should be performed during the EOT +30 Days Visit. Note: The EOT +30 Days Visit does not need to be conducted if the EOT Visit is ≥30 days after the final dose of CORT125281 and/or enzalutamide.

- Record concomitant medications
- Record AEs
- Physical examination
- Measure body weight
- Vital signs
- ECOG performance status
- 12-lead ECGs (performed in triplicate)
- Local laboratory tests (see Table 11 for details)
  - CBC with differential
  - Chemistry, including LDH
  - Urinalysis
- PRO and QoL questionnaires

7.5.2 Every 4 Months After the End-of-Treatment +30 Days Visit (± 10 Days)

- Record post-treatment anticancer therapies, dates of initiation, end dates, and response
- Record survival information (ie, date and cause of death), unless the patient requests to be withdrawn specifically from the study survival follow-up. This request must be documented in the patient's medical record and signed by the Investigator. The study staff may use public information source (such as county records) to obtain information about survival status only per local regulations, as appropriate.
- For patients who discontinued the CORT125281 + enzalutamide due to reasons other than disease progression, continue tumor assessments and PRO and QoL questionnaires per the schedule of procedures until disease progression

7.6 Unscheduled Visits

As appropriate, assessments deemed clinically necessary by the Investigator may be done at unscheduled visits. Sites should enter data from all unscheduled visits in unscheduled eCRFs.

8 SAFETY EVENT DOCUMENTATION AND REPORTING

8.1 Adverse Event

8.1.1 Definition

An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product that emerges or worsens relative to the patient's pre-treatment baseline, whether or not it is considered to be related to the investigational product.

Illnesses present before the patient signs the ICF are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

8.1.2 Performing Adverse Events Assessments

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. The Investigator remains responsible for managing AEs that are serious or that cause a patient to withdraw before completing the study. Frequency of follow-up of any particular AE is left to the discretion of the Investigator. Duration of follow-up and requirements for immediate SAE reporting (within 24 hours of the event) are described below.

Safety results collected during the study (eg, AEs, laboratory test results, physical findings) will be monitored on an ongoing basis by the Medical Monitor and Investigator.

Collection of AEs will start immediately following signing of the ICF and will continue until 30 days after the final dose of study treatment (CORT125281 or enzalutamide, whichever is later). Illnesses present before the patient signs the ICF are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF. New signs or symptoms or worsening in severity of a cancer symptom that occur in association with disease progression should be recorded as AEs. AEs that occur after start of study treatment and up to and including 30 days after administration of the final dose of study treatment will be considered TEAEs. Adverse events reported more than 30 days after the final dose of study treatment will be considered post-treatment AEs.

All AEs will be documented on the AE eCRF and in the patient's medical record. The following attributes must be assigned: (1) description, (2) dates of onset and resolution, (3) severity (see Section 8.1.3), (4) relationship to the study treatment (see Section 8.1.4), (5) "serious" criteria if applicable (see Section 8.2), and (6) action taken. The Investigator will actively solicit this information and assess the AEs in terms of severity and relationship to each study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a unifying diagnosis whenever possible, rather than individual underlying signs and symptoms. The Investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. This treatment may extend beyond the duration of the study. The

Investigator will record treatment and medications required for treatment on the appropriate eCRF(s).

In the event that a patient is withdrawn from the study because of an AE, the event must be recorded on the Termination eCRF as the reason for discontinuation.

All AEs considered to be related (see Section 8.1.4) to study treatment (CORT125281 and/or enzalutamide) and all SAEs will be followed until resolved or until a stable status has been achieved.

All SAEs that are study treatment-related and unexpected (Section 8.1.5) must be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities.

8.1.2.1 Adverse Event Follow-Up and Recording

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Investigator to be lost to follow-up.

AEs will be followed and recorded as described in Table 12.

Table 12 Follow-Up and Recording of Adverse Events and Deaths

Action	Duration of Action		
	From ICF Signature to Start of Treatment (Screening Period)[a]	**From Start of Treatment (Day 1) Through 30-Day Follow-Up Visit (Safety Follow-Up Period)**	**After 30-Day Follow-up Visit**
Record all new AEs in eCRF	Yes	Yes	No
Record all worsening AEs in eCRF	Yes	Yes	No
Follow-up of AEs in eCRF	No[b]	Yes	Yes

AE, adverse event; eCRF, electronic case report form; ICF, informed consent form.
[a.] These AEs will not be considered treatment-emergent AEs (ie, AEs collected from patients who receive study treatment).
[b.] AEs that are ongoing at the start of study will be noted in the Medical History eCRF.

8.1.3 Severity

The seriousness of an AE should not be confused with its severity. To describe the maximum severity of the AE on the AE eCRF, the Investigator will use the NCI-CTCAE, version 4.03 (NCI-CTCAE 2010). For events not listed in the NCI-CTCAE, the definitions from the NCI-CTCAE provided in Table 13 should be used to evaluate the grade of severity for the AE.

Table 13 Adverse Event Grades Based on the Common Terminology Criteria for Adverse Events

Grade	Description
1	**Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	**Moderate:** minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, and managing money)
3	**Severe**: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	**Life-threatening:** Life-threatening consequences; urgent intervention indicated
5	**Death:** Death related to AE

Source: National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (NCI-CTCAE 2010).

8.1.4 Relationship to Study Treatment

The Investigator responsible for the patient's care (or qualified designee) will assess causality of AEs and SAEs based on the causal attribution guidance in Table 14. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). Relationship to study treatment (CORT125281 and/or enzalutamide) will be assessed for all AEs.

Table 14 Causal Attribution Guidance for Adverse Events

Not related	An AE that is judged to be clearly due only to extraneous causes such as diseases, environment, and the like or for which it is temporally implausible to be related to the use of the drug. The cause must be noted on the AE eCRF.
Possibly related	An AE that might be due to the use of the drug. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded. An alternative explanation is inconclusive, eg, concomitant drug(s), concurrent disease(s).
Probably related	An AE that might be due to the use of the drug. The relationship in time is suggestive. An alternative explanation is less likely, eg, concomitant drug(s) or concurrent disease(s).

AE, adverse event; eCRF, electronic case report form.

8.1.5 Expectedness

An AE, regardless of seriousness, is considered unexpected for the study drug (CORT125281) if not reported in the reference safety information (RSI) section of the CORT125281 IB or if the event is of greater severity or frequency than described in the RSI.

Refer to the applicable label for information on expectedness for enzalutamide (for US, Xtandi USPI 2019; for UK, Section 4.8 of the Xtandi SmPC 2017).

8.1.6 Clinical Significance

The Investigator is responsible for determining whether an AE is clinically significant for the patient or the study overall. Clinical significance will be documented in the patient's medical records with the AE information.

8.1.7 Clinical Laboratory Adverse Events

All out-of-range laboratory values will be determined to be clinically significant or not clinically significant by the Investigator. An abnormal laboratory value that leads to a dose modification or patient withdrawal from the study will be recorded as an AE on the eCRF. Other clinically significant laboratory values may be reported as AEs at the discretion of the Investigator.

8.2 Serious Adverse Events

8.2.1 Definition

An SAE is any AE that meets any of the following criteria:

- Results in death (ie, the AE caused or led to the fatality)
- Is life-threatening (ie, the AE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalization or prolongation of existing hospitalization (ie, hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion)
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial reduction of the patient's ability to perform activities of daily living)
- Results in a congenital anomaly or birth defect (ie., an adverse finding in a child or fetus of a patient exposed to the study treatment before conception or during pregnancy)
- Involves other medically important conditions (ie, the AE does not meet any of the above serious criteria but based on appropriate medical judgment, may jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.2 Reporting Serious Adverse Events

Any SAE occurring during the study period (beginning with informed consent) and for at least 30 days after the final dose of study treatment (CORT125281 or enzalutamide, whichever is later) must be reported within 24 hours to the designated safety contact and recorded on the SAE Form. All patients with an SAE must be followed and the outcomes reported. The Investigator

must supply the Sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

Death should be considered an outcome, and not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as progression of cancer under study.

All SAEs occurring from the time of informed consent until 30 days following the last administration of study treatment must be reported to the contact above within 24 hours of the knowledge of the occurrence.

The Investigator (or designee) will complete the SAE reporting form, including whether the event was or was not related to the investigational drug and send to the contact above. The clinical staff will obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient within the patient files.

The Investigator (or designee) will promptly inform the governing IRB/IEC of all serious, unexpected, drug-related events that occur at his or her site or per the IRB/IEC regulations. It is the responsibility of each site to submit Investigational New Drug Safety Reports, as applicable, provided to them by the Sponsor to their IRB or IEC as required by the IRB/IEC, local regulations, and the governing health authorities.

The Investigator (or designee) will fax or email additional follow-up information, if required or available, to the contact above within 24 hours of receipt. This information should be included on a follow-up SAE Form, placed with the original SAE Form, and kept with the appropriate section of the eCRF and/or study patient file.

SAE reporting contact information is provided on the SAE Fax Cover Sheet in the Study Binder.

The Sponsor will ensure that the regulatory authority is informed promptly of Suspected Unexpected Adverse Reactions (SUSAR) for the investigational medicinal product in accordance with US Regulations and EU Directive 2001/20/EC. The reference document used for SUSAR reporting in the United Kingdom will be the most current version of the CORT125281 IB or the SmPC for enzalutamide.

8.2.3 Emergency Sponsor Contact

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of investigational product), study-site personnel will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor.

8.3 Pregnancy

8.3.1 Paternal Exposure

Pregnancy of the patient's partners is not considered to be an AE. The outcome of any conception occurring from the date of the first dose through the EOT Visit should be followed and documented. To capture information about a pregnancy from the partner of a male patient, the Investigator or designee must first obtain the consent of the male patient's partner; the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

9 STATISTICAL METHODS

Detailed procedures for statistical analyses to be performed for this study will be provided in a separate Statistical Analysis Plan that will be finalized before database lock.

9.1 General Statistical Considerations

The key primary and secondary objectives of the study are to determine the MTD and/or biologically active doses of CORT125281 in combination with enzalutamide, and to evaluate safety and tolerability and to characterize preliminary efficacy of CORT125281 in combination with enzalutamide. All study data will be summarized using descriptive statistics. Means, standard deviations, medians, maximum and minimum values will be used to summarize continuous variables. Frequencies and proportions will be used to summarize categorical variables. Time-to-event endpoints will be summarized using Kaplan-Meier method.

In Dose-Determination Phase Segment 1 and in the Expansion Phase, all summaries will be presented by treatment regimen dose group and overall. In the Dose-Determination Phase Segment 2, all analyses will be presented by treatment arm and overall.

Baseline will be defined as the last measurement collected before the first dose of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier).

All analyses will be completed using version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc, Cary, NC).

Detailed procedures for statistical analyses to be performed for this study will be provided in a separate Statistical Analysis Plan that will be finalized before database lock.

9.2 Analysis Populations and Subgroups

The following populations will be defined for this study:

- The Safety Population will include all patients who received at least 1 dose of CORT125281. All safety analyses, except evaluation of DLTs, will be based on the Safety Population.
- The DLT-Evaluable Population will include all patients in the Dose-Determination Phase cohorts who receive at least 1 dose of CORT125281 and fulfill at least 1 of the following:
  1. Complete at least the following durations of study treatment:
     a. Segment 1:28 days of continuous treatment with CORT125281 + enzalutamide
     b. Segment 2: 3 cycles (≥84 days) of CORT125281 + enzalutamide
  2. Experience a DLT within the DLT-evaluation period (Segment 1: 28-days DLT-evaluation period; Segment 2: 3-cycles (≥84-days) 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.
- The Response-Evaluable Population (for ORR) will be the subset of the Safety Population with measurable disease at baseline and at least 1 post-baseline tumor assessment.

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

9.3 Hypothesis Testing

Analyses of safety and anticancer activity for this dose-determination and expansion Phase 1/2a study will focus on estimation of treatment effects via descriptive statistics and CIs Kaplan-Meier methods will be used for time-to-event endpoints.

9.4 Sample Size Calculation

9.4.1 Dose-Determination Phase

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

In Segment 1, an adequate number of DLT-evaluable patients will be enrolled to determine the RD 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 RD.

In Segment 2, approximately 20 patients will be enrolled to obtain 16 DLT-evaluable patients to determine the RD for QD dosing under fed conditions. Patients who discontinue treatment prior to completion of Cycle 3 and are non-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.

9.4.2 Expansion Phase

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 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 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.

9.5 Analysis Plan

9.5.1 Patient Disposition

Patient disposition summaries will include the number of enrolled patients, the number of enrolled patients in each analysis population, the number of patients completing the study per protocol, and the number of patients terminating the study early by the primary reason for discontinuation.

9.5.2 Demographics and Baseline Data

Demographics baseline data will include frequency and percentages for categorical variables, and mean, standard deviation, median, minimum, and maximum for continuous variables. Demographic and baseline characteristics will be summarized by treatment regimen dose group, and overall.

9.5.3 Concomitant Medications

Verbatim terms on eCRFs will be mapped to Anatomical/Therapeutic Chemical class and Generic Drug Names using the most current version of the World Health Organization Drug Dictionary. Concomitant medications will be summarized for all treatment patients by treatment regimen dose group and overall.

9.5.4 Analysis of DLTs

To meet the study primary objective of determining the MTD/ biologically active doses of CORT125281 in combination with enzalutamide, the number, percent and duration of DLTs according to the NCI-CTCAE, version 4.03, will be summarized by CORT125281 dose and overall.

The DLT rate per patient-weeks, defined as the number of DLTs normalized to the total duration of exposure (in weeks) to CORT125281 during the DLT-evaluation period for all patients in the same treatment arm, will also be presented.

Analyses of DLTs will be performed in the DLT-Evaluable Population.

9.5.5 Analyses of Anticancer Activity

The following endpoints will be summarized to meet the study secondary objective of characterizing preliminary efficacy:

- ORR, defined as the proportion of patients with an objective tumor response (either partial response [PR] or complete response [CR] per Investigator using Response Evaluation Criteria in Solid Tumors version 1.1[RECIST v1.1]) in patients with measurable disease, including best radiographic response for soft tissue
- A reduction in PSA level by ≥50%
- Distribution of the best PSA response
- Time to SSE defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression

- rPFS defined as the time from the first dose of study treatment (CORT125281 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. The proportion of patients who are progression-free at 4, 6, and 12 months will also be summarized.
- DOR, defined as the time from the first occurrence of a documented objective tumor response to the time of radiographic progression (per Investigator using RECIST v1.1) or death from any cause on study, whichever occurs first
- Time to PSA progression, clinical progression (per Investigator), and bone disease progression
- Overall survival, defined as the time from the first dose of study treatment (CORT125281 and/or enzalutamide) to the date of death from any cause

Data summaries will include number, percent and waterfall displays as appropriate. Time-to-event endpoints will be characterized using Kaplan-Meier method.

For the analyses of rPFS and DOR, data for the patients who have not experienced disease progression or death will be censored at the time of the last tumor assessment date.

Data for the analysis of overall survival will be censored at the time of the end of follow-up period. Dose adjustments/changes in enzalutamide will be summarized by CORT125281 dose and overall.

The change in markers of disease status, such as PSA and CTCs, will be compared between the Lead-In Period and Cycle 1, when possible.

These analyses will be performed in the Safety Population and Response-Evaluable Population.

9.5.6 Safety Analysis

Safety analyses will be conducted on the Safety Population.

The incidence of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the final dose of study treatment, will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) by SOC and preferred term. Treatment-emergent AEs will be further summarized by severity and relationship to study treatment. For each patient, if multiple incidences of the same AE occur, the maximum severity reported will be used in summaries.

All AEs (whether TEAEs or not) will be listed by individual patient, including information regarding onset, duration, severity, and relationship to study treatment (CORT125281 or enzalutamide). Serious AEs and AEs that led to withdrawal from the study will be listed by individual patient.

The following adverse events will be summarized separately: AEs leading to withdrawal of study treatment (CORT125281 or enzalutamide), dose reduction or interruption, Grade 3 or greater AEs, and SAEs.

All deaths and causes of deaths will be summarized and listed.

Clinical laboratory test results, vital sign measurements, and abnormal ECG values will be summarized overall and for each treatment regimen dose group by parameter, visit, and time

point using descriptive statistics, to include the change from baseline values. Shift tables will be constructed that describe changes from baseline to the end of treatment.

By-patient safety listings will be provided.

9.5.7 Pharmacokinetic Analyses

The plasma PK of CORT125281, enzalutamide, and major metabolites, including M2 will be characterized using non-compartmental analysis, and analyte concentration versus time plots will be provided. PK parameters listed in Table 15 will be calculated, whenever possible, from plasma concentrations of CORT125281, enzalutamide, and M2, and combined exposure to both enzalutamide and M2.

Table 15 PK Variables for Analysis

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

C_{last}, last measurable concentration.

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 obtained 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.

Concentration data and PK parameters will be tabulated and summarized using descriptive statistics. PK relationships to measures of efficacy or toxicity may also be explored. Additional PK analyses may be performed, as deemed appropriate.

The PK of CORT125281, the natural log (ln) transformed C_{max}, $AUC_{0\text{-t}}$, and AUC_{inf}, and other PK parameters will be analyzed by analysis of variance (ANOVA) adjusted for food effect and other potential factors that may influence the outcome. The fed state versus fasted state comparison for C_{max}, $AUC_{0\text{-t}}$, and AUC_{inf} will be carried out using 90% CIs for the ratios of these parameters based on the models. If the 90% CIs are contained within the limits 0.80 to 1.25, lack of substantial food effect will be inferred. The T_{max} values between the fed and fasted state will be compared using non-parametric tests.

9.6 Exploratory Analyses

Exploratory analyses will characterize PRO and QoL using the following endpoints:

- Median time to deterioration defined as ≥10-point decrease from baseline on the overall FACT-P score
- Change from baseline in the overall FACT-P scores, as well as its subscales measuring physical and emotional well-being, prostate-cancer specific QoL, and pain-related score
- Percentage of patients who filled out the survey and showed improvement in FACT-P score, and its subscales

Additional exploratory analyses to evaluate the effects of CORT125281 and enzalutamide on pain and time to worsening of pain will be prespecified in the Statistical Analysis Plan.

The distribution of time to deterioration will be summarized using the Kaplan-Meier method. The change from baseline in the FACT-P score will be analyzed using paired t test. The percentage of patients who show improvement will be summarized.

Changes from baseline in PD variables will be summarized descriptively and exploratory analyses of trends with dose and time may be conducted. The baseline value is defined as the last measurement before the beginning of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier) administration. The relationship between drug concentration variables and PD variables may be explored. The dependence of observations from the same patient may be appropriately taken into account in all of the above analyses.

Exploratory analyses will include assessment of the relationship of pre-treatment tumor GR expression by IHC with clinical outcome and assessment of the scoring method/threshold that is most predictive of response may be detailed separately. These analyses will include analyses of changes in GR expression assessed by IHC and will compare pre- and post-treatment to assess changes over time as potential markers of sensitivity and resistance. The relationship between drug concentration variables and blood cortisol and ACTH will be assessed, in addition to the relationship with clinical outcomes.

9.7 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
- Prior treatment with abiraterone
- Enzalutamide resistant
- ARV7 positive and ARV7 negative (defined by positive on CTC and/or liquid biopsy, or most current definition at the completion of the study)
- GR positive and GR negative (defined by IHC and/or CTCs)

9.8 Data Review Committee

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

the completion of each cohort during the 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. 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.

9.9 Interim Safety Analyses

In Dose-Determination Segment 1, the DRC will make recommendations regarding escalation to the next planned dose, repeating a prior dose, or investigating other dose cohorts (ie, intermediate or lower doses) until the MTD/RD is identified (Section 5.4.1). If a biologically active dose is determined as defined by the dose level at which CORT125281 has been demonstrated to inhibit GR and at which the DLT rate is <33%, the Dose-Determination Phase may be completed prior to the determination of the MTD, per the recommendation of the DRC.

In Dose-Determination Phase Segment 2 (Section 5.4.2), 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 (number of DLTs per week [7-day period] during the DLT-evaluation period), and overall tolerability to determine the feasibility of the dose titration regimen for the Phase 2 RD.

In the Expansion Phase, an interim safety analysis will be conducted after a total of 20 patients complete 3 cycles of therapy.

10 ETHICAL AND LEGAL CONSIDERATIONS

10.1 Compliance with IRB/IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 Code of Federal Regulations [CFR] Part 56.103), IEC regulations, or applicable local regulations. The protocol, ICFs, recruitment materials, and all patient materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled, and the Investigator must submit written approval to the Sponsor, before enrolling any patient. The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB or IEC on receipt of amendments and annually, as local regulations require.

All changes to the consent form must be approved by the IRB/IEC; a determination will be made regarding whether previously consented patients need to be re-consented

The Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the Investigator should be provided to the Sponsor.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

10.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

The Investigator will ensure that the study procedures outlined in this protocol will be conducted in accordance with applicable country and local regulations.

10.3 Protection of Human Patients

10.3.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative.

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

- The ICF will contain all of the elements required by ICH guidelines for GCP and any additional elements required by local regulations.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, samples may be retained for

future determination of active metabolite concentrations and possible biomarkers related to drug response.

- The patient's signed and dated ICF must be obtained before conducting any study procedures.
- The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, blood, plasma, serum, and tissue samples may be obtained for future analysis to help identify biomarkers of disease or CORT125281 treatment.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

10.3.2 Patient Confidentiality

To maintain patient privacy, all source documents, study reports, and communications will identify the patient by the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original study records for verification of data gathered on source documents and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations.

10.3.3 Patient Privacy

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the Sponsor, regulatory agencies, and IRB/IEC/Research Ethics Board. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations from each patient or, if appropriate, the patient's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient, and the patient will be removed from the study.

Written authorization is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Study Monitoring

Monitoring of the study site will be performed by the Sponsor's Clinical Monitor or designee.

- Monitoring will be performed in accordance with applicable federal regulations and guidance.
- Monitoring will include regular site visits and communication with the Investigator and site staff as appropriate to discuss and answer study questions; ensure compliance with the protocol; and ensure quality and integrity of the data.
- Monitors will ensure the site maintains an adequate supply of investigational products; any necessary supplies and ensure that appropriate storage conditions are maintained.
- Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312; and ICH Guideline for GCP.

11.2 Quality Management

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance audit during the study by the Sponsor or its designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory agencies at their discretion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (eg, GLP, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

11.3 Documentation

11.3.1 Electronic Case Report Forms and Study Records

The Investigator must generate and maintain complete, adequate, accurate, reliable, and consistent records to enable full documentation of study conduct. Study data will be captured on eCRFs. Investigators must retain all original source documents, and the Sponsor or its designee will notify Investigators in writing when the trial-related records are no longer needed.

11.3.2 Access to Source Documentation

The Sponsor or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct.

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB/IEC may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, x-rays, workbooks, patients' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

11.3.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as x-rays, laboratory tests, and ECGs. All data entered into the eCRFs must be substantiated by a source document.

11.3.4 Study Files and Retention of Study Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor before disposing of any study records.

11.4 Long-Term Retention of Biological Samples

All biological samples will be retained by the Sponsor or designee under the original informed consent of the patient and the IRB/IEC approval. Samples will be held for a period up to 10 years after acquisition. The Sponsor or the designee may store the patient's sample(s) for longer if required to address regulatory agency questions; in this event, the patient's sample(s) will be destroyed after all questions are adequately answered.

An individual patient can choose to withdraw consent to have his samples stored for future research at any time without affecting their participation in the study or their care by the health provider. Upon receipt of a request for sample destruction, that patient's sample(s) will then no longer be used for research purposes, and their sample(s) will be destroyed. However, if there are ongoing regulatory questions, the patient's sample(s) will be destroyed after all questions are adequately answered.

The long-term samples retained will be coded to allow de-identification according to applicable regulatory guidelines. It is the responsibility of the trial site to ensure that samples are appropriately labeled in accordance with trial procedures to comply with all applicable laws, which may include but are not limited to European Directives 95/46/EC and 2002/58/EC and any legislation and/or regulatory implementing or made pursuant to them, or which amends, replaces, re-enacts, or consolidates any of them, and all other applicable laws relating to processing of personal data and privacy that may exist in any relevant jurisdiction. Biological samples collected from participants as part of this trial will be transported, stored, accessed, and processed in accordance with all applicable laws relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

11.5 Clinical Supplies

11.5.1 Inventory, Reconciliation, Return, and Disposition of Clinical Supplies

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures. Storage of study drug is described in Table 1.

11.5.2 Clinical Supply Inventory

A detailed inventory must be completed for all study drug. The study drug is to be used in accordance with the protocol by patients who are under the direct supervision of an Investigator. The study drug must be dispensed only by an appropriately qualified person to patients in the study.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of study drug received, patients to whom study drug is dispensed (patient by-patient dose specific accounting), and study drug lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (on-site clinical research associate) has confirmed the accountability data and Sponsor has approved return or destruction.

11.5.3 Return or Disposal of Study Drug and/or Supplies

All clinical study drug and/or supplies will either be destroyed by the site per institutional policy or be returned to the Sponsor or designee for destruction.

Unused study drug may be destroyed on site, per the site's SOPs, but only after Sponsor or designee has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process, before study drug destruction. All study drug destroyed on site must be documented.

Documentation must be provided to Sponsor and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to Sponsor upon request.

11.6 Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of study treatment disposition is maintained. It is the responsibility of the Investigator to ensure that the study treatments are used only in accordance with the approved protocol. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition), patient dispensing records, and returned or destroyed study drug. Dispensing records will document quantities received from the Sponsor (or designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, and the initials of the person dispensing the study treatments. At the end of the study, after final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to standard procedures.

11.7 Noncompliance with the Protocol

Prospective approval of deviations from the inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study-site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6.

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor in writing and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study patients. When a deviation from the protocol is deemed necessary for an individual patient, the Investigator must obtain approval in writing from the Sponsor.

Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the patient and/or the study.

Any significant protocol deviations affecting patient eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

11.8 Financial Disclosure

Investigators will be required to disclose any financial equity interests in the Sponsor and any conflicts of interest, as defined by the Sponsor.

11.9 Publication and Disclosure Policy

Corcept, as the Sponsor, has a proprietary interest in this study.

No individual publications will be allowed before publication of the multicenter results except as agreed with the Sponsor. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review before submission to the publisher.

The Sponsor will comply with the requirements for publication of study results and determination of authorship in accordance with standard editorial and ethical practice and with the International Committee of Medical Journal Editors requirements.

11.10 Final Report Signature

The clinical study report Coordinating Investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study. The Sponsor will select a qualified Investigator from among Investigators participating in the design, conduct, and/or analysis of the study to serve as the clinical study report Coordinating Investigator. The Sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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APPENDIX A: SCHEDULE(S) OF ASSESSMENTS

Table 16 Overall Schedule of Assessments

Study Period	Screening	Lead-In Period [a]	Combination Treatment Period (28-Day Cycles) [b]								End of Treatment	Post-Treatment Follow-Up [c]	
Cycle	Screening	Cycle 1	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 3	Cycle 4 & Beyond [b]	Every 3 Cycles from Cycle 3	EOT	EOT +30 Days	Every 4 Mnth
Day		Day -28 or Day -7	Day 1	Day 8	Days 15 & 22	Day 1	Day 15	Day 1	Day 1	Day 1			
Visit Window			± 1 Day	± 1 Day	± 1 Day	± 3 Days	± 3 Days	± 3 Days	± 3 Days	± 3 Days			± 10 Days
Written informed consent	X												
Tumor biopsy	X [d]					X[d]							
Review inclusion/ exclusion criteria	X	X [e]	X [e]										
Record medical and oncology history	X	X [e]	X [e]										
Record prior medications	X	X [e]	X [e]										
Record concomitant medications		X	X [f]	X	X	X	X	X	X		X	X	X
Record adverse events	X	X	X [f]	X	X	X	X	X	X		X	X	
Physical examination [g]	X	X	X [f]	X	X	X	X	X	X		X	X	
Measure height	X												
Measure body weight	X	X	X			X		X	X		X	X	
Vital signs	X	X	X	X	X	X	X	X	X		X	X	
ECOG performance status	X	X	X [f]	X	X	X	X	X	X		X	X	
12-lead ECG (triplicate)	X		X [h]		X [h]			X [h]				X	
CBC with differential [i]	X [j]		X [f]	X	X	X	X	X	X		X	X	
Chemistry, including LDH	X [j]		X [f]	X	X	X	X	X	X		X	X	
Serum amylase and lipase	X		X	X	X	X	X	X		X [k]			

Study Period	Screening	Lead-In Period [a]	Combination Treatment Period (28-Day Cycles) [b]								End of Treatment	Post-Treatment Follow-Up [c]	
Cycle	Screening	Cycle 1	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 3	Cycle 4 & Beyond [b]	Every 3 Cycles from Cycle 3	EOT	EOT +30 Days	Every 4 Mnth
Day		Day -28 or Day -7	Day 1	Day 8	Days 15 & 22	Day 1	Day 15	Day 1	Day 1	Day 1			
Visit Window			± 1 Day	± 1 Day	± 1 Day	± 3 Days	± 3 Days	± 3 Days	± 3 Days	± 3 Days			± 10 Days
PT, aPTT, and INR	X [j]		X [f]			X		X			X		
Urinalysis	X [j]		X [f]			X		X		X	X	X	
TSH, with reflex FT4 and TT3/FT3	X [j]							X [l]					
Hepatitis B and C serologies and HIV	X												
Pharmacodynamic sampling [m]													
Whole blood sample pharmacogenomics testing (Dose-Determination Segment 1 only)	X												
Pharmacokinetic blood samples [n]													
Radiographic tumor assessment: CT/MRI, and bone scan [o, p]	X [o]					X			X		X		
Tumor markers: PSA	X		X			X		X	X		X		
PRO and QoL assessments [q]		X	X					X		X		X	X
Dispense study treatment [r]		X	X			X		X	X				
Provide diary card		X	X			X		X	X				
Study treatment accountability			X			X		X	X		X		
Survival follow-up													X [s]

aPTT, activated partial thromboplastin time; CBC, complete blood count; CT, computed tomography; DRC, Data Review Committee; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FT3, free triiodothyronine; FT4, free thyroxine; INR, international normalized ratio; LDH, lactic dehydrogenase; Mnth, month; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PRO, patient-reported outcomes; PT, prothrombin time; QoL, quality of life; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine.

Note: In all parts of the study, a cycle of therapy is considered to be 28 days with no rest periods in between cycles. All procedures within a cycle should be counted by calendar day from Day 1 of that cycle. A 2-day window will be allowed for study visits.

[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. When a recommended dose of enzalutamide is determined by the DRC, the DRC may recommend discontinuing the lead-in for subsequent cohorts.

[b.] Upon discontinuation of CORT125281, if the patient continues on enzalutamide alone (Section 5.7.1.1) and all toxicities attributed to CORT125281 have resolved, visit frequency can be decreased per the Investigator's standard of care. The patient should come for their regularly scheduled visit (the subsequent cycle) after discontinuing CORT125281. After this visit, visits can be conducted less frequently per Investigator discretion, but at a minimum every 3 cycles while on enzalutamide alone; at these visits they will have the assessments listed in the "Cycle 4 & Beyond" column. After discontinuation of enzalutamide, the patient will return for their EOT Visit, and then for an EOT +30 Days Visit.

[c.] Phone follow-up for overall survival (ie, the date and cause of death, and post-treatment information) will continue every 4 months until the study endpoints are met or 2 years from the date that the last patient enrolls in the study (whichever is later).

[d.] Consent to provide optional or mandatory (for a subset of patients) paired tissue biopsy material for determination of glucocorticoid receptor expression and other exploratory biomarkers is required for eligibility; the first biopsy will be obtained within 6 weeks prior to the first dose of study treatment (enzalutamide and/or CORT125281). An additional paired biopsy will be collected at Cycle 2 Day 1 (-14 days). It is preferred that this biopsy be collected from the same lesion as the baseline sample, if sufficient tissue remains and if logistically feasible. Optional: consent to provide on-study biopsy 1) obtained during procedure conducted as standard of care; or 2) at the time of disease progression.

[e.] To be performed on Cycle 1 Day -28 for patients enrolled in Cohort 1 of Dose-Determination Phase Segment 1 with lead-in, Cycle 1 Day -7 for patients enrolled in the Expansion Phase Food-Effect Subcohort, and Cycle 1 Day 1 for non-food-effect patients enrolled in the Abi-Resistant and ARant-Resistant Cohorts of the Expansion Phase.

[f.] To be performed and reviewed prior to the first dose of CORT125281. Laboratory assessments (CBC with differential, chemistry [including LDH], PSA, and urinalysis) may be collected on either Cycle 1 Day -1 or Cycle 1 Day 1 based upon logistics and convenience to the sites and patients.

[g.] Complete physical examinations should be performed at Screening, Day 1 of each cycle, and the End-of-Treatment Visit. Limited physical examinations should be performed at all other visits.

[h.] 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).

[i.] Complete blood count will also be used to assess the neutrophil-to-lymphocyte ratio and relative abundance of other cells.

[j.] Screening safety laboratory assessments must be performed within 7 days of the start of the Lead-In Period. For patients who are NOT participating in the Lead-In Period, Screening CBC and chemistry do not need to be repeated if they were collected within 7 days of Cycle 1 Day 1.

[k.] Every 3 months until completion of 12 months of study treatment, starting on Cycle 6 Day 1. Note: For patients continuing on enzalutamide alone, sample collections for amylase and lipase will not be required at these visits.

[l.] Every 3 months for the first year starting with Cycle 3 Day 1 and after 1 year the frequency will decrease to once every 6 months.

[m.] Refer to Table 17 (Dose-Determination Phase Segment 1), Table 18 (Dose-Determination Phase Segment 2), and Table 19 (Expansion Phase) for detailed pharmacodynamic sample schedules.

[n.] Refer to Table 20 (Dose-Determination Phase Segment 1), Table 21 (Dose-Determination Phase Segment 2), and Table 22 (Expansion Phase) for detailed pharmacokinetic sample schedules.

[o.] Isolated new lesions on bone scan at <12 weeks from Cycle 1 Day 1 will be confirmed with a repeat bone scan at 6 weeks to rule out bone scan flare: refer to Prostate Cancer Clinical Trials Working Group 3 for 2+2 rule.

[p.] Tumor assessments (CT/MRI, bone scan): The baseline tumor assessment should be performed within 28 days prior to the first dose of enzalutamide (for Dose-Determination Phase Segment 1) and/or CORT125281 (for Dose-Determination Phase Segment 2 and the Expansion Phase). The first on-study tumor assessment should be performed 8 weeks from the first dose of study treatment (CORT125281 or on-study enzalutamide, whichever is earlier) and then every 8 weeks for the first 24 weeks and every 12 weeks thereafter, at the EOT Visit (if not performed within 4 weeks), and as clinically indicated. For on-study scans, a window of ±14 days is acceptable with the timing of the scans based on Cycle 1 Day 1.

[q.] Includes FACT-P and questions relating to patient-reported pain. To be performed prior to dose during the following visits: Prior to initiation of CORT125281 and/or enzalutamide, at the completion of the Lead-In Period (applicable to patients in Dose-Determination Phase Segment 1 and patients in the Expansion Phase for whom food-effect will be assessed), Cycle 3 Day 1, every 3 cycles after Cycle 3 Day 1, and at the End-of-Treatment +30 Days Visit. For patients who discontinue treatment prior to disease progression, the questionnaires will be performed per the Schedule of Assessments until unequivocal progressive disease is documented.

[r.] For patients in Dose-Determination Phase Segment 2, the patient will take their current dose of CORT125281 in the clinic on Cycle 1 Day 1, Cycle 1 Day 15, and the day before their second dose escalation (eg, Cycle 2 Day 1 or Cycle 2 Day 15). If the patient tolerates the current dose and escalation/titration of the dose occurs, the first day of the increased dose will be on the day following the study visit. For patients in the Expansion Phase Food-Effect Subcohort, enzalutamide dosing will begin on Cycle 1 Day 2.

[s.] Record post-treatment anticancer therapies, dates of initiation, and end dates, and response.

Table 17 Pharmacodynamic Schedule of Assessments, Dose-Determination Phase Segment 1

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
ACTH, cortisol	Blood	Screening, Cycle 1 Day 1 [a], Cycle 1 Day 15, Cycle 3 Day 1, Every 3 cycles from Cycle 3 [b], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Fasting sample collected between 7 a.m. to 9 a.m. Analysis of ACTH by radioimmunoassay and cortisol by mass spectroscopy by central laboratory
GC-related gene panel	Blood	Screening, Cycle 1 Day 1 [a], Cycle 1 Day 15, Cycle 3 Day 1, Every 3 cycles from Cycle 3 [b], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Fasting sample collected between 7 a.m. to 9 a.m. at the same time as the cortisol and ACTH samples; mRNA expression by technologies such as NanoString
DHEA-S, androstenedione, estradiol and free and total testosterone	Blood	Screening, Cycle 1 Day 1 [a], Cycle 1 Day 15	Fasting sample collected between 7 a.m. to 9 a.m. Analysis by mass spectroscopy by central laboratory
GR expression, ARV7, CTC enumeration, and exploratory markers	CTC	Screening, Cycle 1 Day 1 [a]; Cycle 2 Day 1 Cycle 3 Day 1 Cycle 4 Day 1 Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Serial assessment of CTC number and biomarkers for response, prognosis, and to identify correlative markers of sensitivity, Example biomarkers include ARV7 protein immunofluorescent assay or GR IHC run on the [redacted] Platform
GR expression, ARV7, and exploratory markers	Paired tumor biopsies	Screening Cycle 2 Day 1 [d]	Formalin fixed, paraffin embedded tissue sample; includes IHC for GR [redacted] and the mRNA expression of genes involved in tumor GR-signaling, resistance, apoptosis, and metabolism
Circulating tumor DNA and saved sample for exploratory biomarkers	Blood	Screening, Cycle 1 Day 1 [a], Cycle 3 Day 1, Every 3 cycles from Cycle 3 [b], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Detect aberrations that may be associated with therapeutic resistance including AR amplification

ACTH, adrenocorticotrophic hormone; AR, androgen receptor; ARV7, androgen-receptor splice variant 7 messenger RNA; CTC, circulating tumor cell; DHEA-S, dehydroepiandrosterone-sulfate; DNA, deoxyribonucleic acid; GC, glucocorticoid; GR, glucocorticoid receptor; IHC, immunohistochemistry; mRNA, messenger RNA.

[a.] The Cycle 1 Day 1 sample should only be collected for patients with a lead-in of enzalutamide alone prior to the first dose of CORT125281.

[b.] After 1 year, the sampling frequency will decrease to every 6 months.

[c.] If patients discontinue study treatment for reasons other than disease progression, the sample will be collected upon disease progression.
[d.] Paired biopsies collected with the first biopsy obtained within 6 weeks prior to initiating study treatment (CORT125281 or on-study enzalutamide, whichever is earlier). Soft tissue biopsy is preferred, when possible. Optional: consent to provide additional on-study biopsy (1) obtained during procedure conducted as standard of care; or (2) at the time of disease progression.

Table 18 Pharmacodynamic Schedule of Assessments, Dose-Determination Phase Segment 2

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
ACTH, cortisol	Blood	Cycle 1 Day 1, Cycle 1 Day 15, 2 weeks (±2 days) after each dose escalation [a], Every 3 cycles from Cycle 3 [b], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Fasting sample collected between 7 a.m. to 9 a.m pre-dose Analysis of ACTH by radioimmunoassay and cortisol by mass spectroscopy by central laboratory. Assessments may include related analytes such as 11-deoxycortisol or testosterone.
GC-related gene panel	Blood	Cycle 1 Day 1[d], Cycle 1 Day 2, Cycle 1 Day 15, 2 weeks (±2 days) after each dose escalation [a], Every 3 cycles from Cycle 3 [a], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Fasting sample collected between 7 a.m. to 9 a.m pre-dose, at the same time as the cortisol and ACTH samples mRNA expression by technologies such as NanoString Cycle 1 Day 1: additional collection at 4 hours post-dose (not fasted)
GR expression, ARV7, CTC enumeration, and exploratory markers	CTC	Cycle 1 Day 1, Cycle 1 Day 15, 2 weeks (±2 days) after each dose escalation [a], Every 3 cycles from Cycle 3 [b], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Serial assessment of CTC number and biomarkers for response, prognosis, and to identify correlative markers of sensitivity, Example biomarkers include ARV7 protein immunofluorescent assay or GR IHC run on the [redacted] Platform
GR expression, ARV7, and exploratory markers	Paired tumor biopsies	Screening Cycle 3 Day 1 [e]	Formalin fixed, paraffin embedded tissue sample; includes IHC for GR [redacted] and mRNA expression of genes involved in tumor GR-signaling, resistance, apoptosis, and metabolism
Circulating tumor DNA and saved sample for exploratory biomarkers	Blood	Cycle 1 Day 1, Cycle 1 Day 15, 2 weeks (±2 days) after each dose escalation [a], Every 3 cycles from Cycle 3 [b], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Detect aberrations that may be associated with therapeutic resistance including AR amplification
Spot urine (cortisol and creatinine) [f]	Urine	Cycle 1 Day 1, Cycle 1 Day 15, 2 weeks (±2 days) after each dose escalation [a], Every 3 cycles from Cycle 3 [b], Upon discontinuation (+7 days) of CORT125281, Disease progression [c]	Cortisol and creatinine analysis by mass spectrometry by central laboratory. Assessments may include related analytes such as THS

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
24-hour UFC (cortisol and creatinine) [f]	Urine	Screening [f], The day before the spot urine collection [f]	UFC with creatinine will be measured by tandem mass spectrometry by central laboratory. Assessments may include related analytes such as THS

ACTH, adrenocorticotrophic hormone; AR, androgen receptor; ARV7, androgen-receptor splice variant 7 messenger RNA; CTC, circulating tumor cell; DHEA-S, dehydroepiandrosterone-sulfate; DNA, deoxyribonucleic acid; GC, glucocorticoid; GR, glucocorticoid receptor; IHC, immunohistochemistry; mRNA, messenger RNA; THS, tetrahydrodeoxycortisol; UFC, urinary free cortisol.

[a.] Must be collected after maintaining the CORT125281 dose for 14 days and prior to any dose modification. It is recommended, but not required, to schedule PD sample collections to coincide with the PK collection days.

[b.] After 1 year, the sampling frequency will decrease to every 6 months.

[c.] If patients discontinue treatment for reasons other than disease progression, the sample will be collected upon disease progression.

[d.] Both pre-dose (fasted) and 4 hr post-dose (not fasted).

[e.] Paired biopsies collected with the first biopsy obtained within 6 weeks prior to initiating CORT125281. Soft tissue biopsy is preferred, when possible. Optional: consent to provide additional on-study biopsy (1) obtained during procedure conducted as standard of care; or (2) at the time of disease progression.

[f.] Spot urine test will be conducted during the scheduled visit. The 24-hour UFC will be collected at home the day prior to the visit. The Screening 24-hour UFC sample can be collected anytime between Screening and the first dose of CORT125281.

Table 19 Pharmacodynamic Schedule of Assessments, Expansion Phase

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
ACTH, cortisol	Blood	Cycle 1 Day 1, Cycle 1 Day 15, Every 3 cycles from Cycle 3 [a], Upon discontinuation (+7 days) of CORT125281, Disease progression [b]	Fasting sample collected between 7 a.m. to 9 a.m pre-dose Analysis of ACTH by radioimmunoassay and cortisol by mass spectroscopy by central laboratory. Assessments may include related analytes such as 11-deoxycortisol or testosterone.
GC-related gene panel	Blood	Cycle 1 Day 1 [c], Cycle 1 Day 2, Cycle 1 Day 15, Every 3 cycles from Cycle 3 [a], Upon discontinuation (+7 days) of CORT125281, Disease progression [b]	Fasting sample collected between 7 a.m. to 9 a.m pre-dose, at the same time as the cortisol and ACTH samples; mRNA expression by technologies such as NanoString Cycle 1 Day 1: additional collection at 4-hour post-dose (not fasted)
GR expression, ARV7, CTC enumeration, and exploratory markers	CTC	Cycle 1 Day 1, Cycle 2 Day 1, Every 3 cycles from Cycle 3 [a], Upon discontinuation (+7 days) of CORT125281, Disease progression [b]	Serial assessment of CTC number and biomarkers for response, prognosis, and to identify correlative markers of sensitivity, Example biomarkers include ARV7 protein immunofluorescent assay or GR IHC run on the [redacted] Platform
GR expression, ARV7, and exploratory markers	Paired tumor biopsies	Screening Cycle 2 Day 1 [d]	Formalin fixed, paraffin embedded tissue sample; includes IHC for GR [redacted] and the mRNA expression of genes involved in tumor GR-signaling, resistance, apoptosis, and metabolism
Circulating tumor DNA and saved sample for exploratory biomarkers	Blood	Cycle 1 Day 1, Cycle 2 Day 1, Every 3 cycles from Cycle 3 [a], Upon discontinuation (+7 days) of CORT125281, Disease progression [b]	Detect aberrations that may be associated with therapeutic resistance including AR amplification
Spot urine (cortisol and creatinine) [e]	Urine	Cycle 1 Day 1, Cycle 2 Day 1, Every 3 cycles from Cycle 3 [a], Upon discontinuation (+7 days) of CORT125281, Disease progression [b]	Cortisol and creatinine analysis by mass spectrometry by central laboratory. Assessments may include related analytes such as THS
24-hour UFC (cortisol and creatinine) [e]	Urine	Screening, Cycle 1 Day 22	UFC with creatinine will be measured by tandem mass spectrometry by central laboratory. Assessments may include related analytes such as THS

ACTH, adrenocorticotrophic hormone; AR, androgen receptor; ARV7, androgen-receptor splice variant 7 messenger RNA; CTC, circulating tumor cell; DHEA-S, dehydroepiandrosterone-sulfate; DNA, deoxyribonucleic acid; EOT, End-of-Treatment; GC, glucocorticoid; GR, glucocorticoid receptor; IHC, immunohistochemistry; mRNA, messenger RNA; THS, tetrahydrodeoxycortisol; UFC, urinary free cortisol.

a. After 1 year, the sampling frequency will decrease to every 6 months.

b. If patients discontinue CORT125281 for reasons other than disease progression, the sample will be collected upon disease progression.

[c.] Both pre-dose (fasted) and 4 hr post-dose (not fasted).
[d.] Paired biopsies collected with the first biopsy obtained within 6 weeks prior to initiating CORT125281/enzalutamide. Soft tissue biopsy is preferred, when possible. Optional: consent to provide additional on-study biopsy (1) obtained during procedure conducted as standard of care; or (2) at the time of disease progression.
[e.] Spot urine test will be conducted during the scheduled visit. The 24-hour UFC sample will be collected at home the day prior to the visit. The Screening 24-hour UFC sample can be collected anytime between Screening and the first dose of CORT125281.

Table 20 Pharmacokinetic Schedule of Assessments, Dose-Determination Phase Segment 1

PK Sample	Day	Nominal Time	Window
Enzalutamide	Cycle 1 Day -1 (Lead-in)	0 hour, pre-dose	Within 15 minutes before the morning dose of enzalutamide
		30 minutes	Within 5 minutes of nominal time
		1 hour	
		1.5 hours	±10 minutes
		2 hours	
		3 hours	
		4 hours	
		6 hours	
		8 hours	
		12 hours	±30 minutes
		24 hours [a], pre-dose	
CORT125281 & Enzalutamide	Cycle 1 Day 1	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		30 minutes	Within 5 minutes of nominal time
		1 hour	
		1.5 hours	±10 minutes
		2 hours	
		3 hours	
		4 hours	
		6 hours	
		8 hours	
		12 hours	±30 minutes
		24 hours [a], pre-dose	

PK Sample	Day	Nominal Time	Window
CORT125281 & Enzalutamide	Cycle 1 Day 22	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		2 hours	±10 minutes
CORT125281 & Enzalutamide	Cycle 2 Day 1	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		30 minutes	Within 5 minutes of nominal time
		1 hour	
		1.5 hours	±10 minutes
		2 hours	
		3 hours	
		4 hours	
		6 hours	
		8 hours	
		12 hours	±30 minutes
CORT125281 & Enzalutamide	Cycle 2 Day 15	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		2 hours	±10 minutes
CORT125281 & Enzalutamide	Cycle 3 Day 1	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		2 hours	±10 minutes
CORT125281 [b]	Intra-patient dose escalation: On current dose and 4 weeks following dose adjustment	0 hour, pre-dose	Within 15 minutes before the morning dose of CORT125281
		2 hours	±10 minutes
Enzalutamide [b]	Intra-patient dose escalation: On current dose and 4 weeks following dose adjustment	0 hour, pre-dose	Within 15 minutes before the morning dose of enzalutamide
		2 hours	±10 minutes

Note: On all days with pharmacokinetic assessments, CORT125281 and enzalutamide should be taken at the same time in the clinic. Both the times of the previous day's doses of CORT125281 and enzalutamide and the times of the current day's doses should be recorded.

[a.] The Cycle 1 Day -1 24-hour enzalutamide sample and the Cycle 1 Day 1 pre-dose sample may be a single sample, if the timepoints align. The Cycle 1 Day 1 24-hour sample should be taken prior to dosing on Cycle 1 Day 2.

[b.] Patients who undergo intra-patient dose escalation of CORT125281.

Table 21 Pharmacokinetic Schedule of Assessments – Dose-Determination Phase Segment 2

PK Sample	Day	Nominal Time[a]	Window
CORT125281 & Enzalutamide	Cycle 1 Day 15	0 hour, pre-dose	Within 15 minutes before the dose of study treatment
		1 hour	±10 minutes
		2 hours	
		3 hours	
		4 hours	
		6 hours [b]	
CORT125281 & Enzalutamide	2 weeks (±2 days) after each dose escalation [c]	0 hour, pre-dose	Within 15 minutes before the dose of study treatment
		1 hours	±10 minutes
		2 hours	
		3 hours	
		4 hours	
		6 hours [b]	
CORT125281 [d]	After a patient dose reduces and maintains dose for 2 weeks (±2 days) [d]	0 hour, pre-dose	Within 15 minutes before the dose of study treatment
		1 hour	±10 minutes
		2 hours	
		3 hours	
		4 hours	

PK, pharmacokinetic.

Note: On all days with PK assessments, CORT125281 and enzalutamide should be taken at the same time in the clinic. Both the times of the previous day's doses of CORT125281 and enzalutamide and the times of the current day's doses should be recorded.

[a.] Nominal times are relative to the dose of study treatment (both CORT125281 and enzalutamide).

[b.] The 6-hour PK timepoint may be omitted based upon available PK data.

[c.] Must be collected after maintaining the CORT125281 dose for 14 days and prior to any dose modification.

[d.] This sample only applies to those patients who require a dose reduction of CORT125281 (see Section 5.7.1) and must be collected prior to further dose modification.

Table 22 Pharmacokinetic Schedule of Assessments, Expansion Phase

PK Sample	Day	Nominal Time	Window
Both Expansion Cohorts			
CORT125281 & Enzalutamide	Cycle 2 Day 1	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		2 hours	±10 minutes
CORT125281 & Enzalutamide	Cycle 3 Day 1	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		2 hours	±10 minutes
Abi-Resistant Cohort Food-Effect Subcohort Only [a]			
CORT125281	Cycle 1 Day -7	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		30 minutes	Within 5 minutes of nominal time
		1 hour	
		1.5 hours	±10 minutes
		2 hours	
		3 hours	
		4 hours	
		6 hours	
		8 hours	
		12 hours [b]	±30 minutes
		24 hours	

PK Sample	Day	Nominal Time	Window
CORT125281	Cycle 1 Day 1	0 hour, pre-dose	Within 15 minutes before the morning dose of study treatment
		30 minutes	Within 5 minutes of nominal time
		1 hour	
		1.5 hours	±10 minutes
		2 hours	
		3 hours	
		4 hours	
		6 hours	
		8 hours	
		12 hours [b]	±30 minutes
		24 hours, pre-dose	

PK, pharmacokinetic.
Note: On all days with PK assessments, CORT125281 and enzalutamide should be taken at the same time in the clinic. Both the times of the previous day's doses of CORT125281 and enzalutamide and the times of the current day's doses should be recorded.
[a.] Only for 10 patients enrolled in the Abi-Resistant Cohort.
[b.] The 12-hour PK timepoint may be omitted based upon available PK data.
[c.] The Cycle 1 Day 1 24-hour sample should be taken prior to dosing on Cycle 1 Day 2.

APPENDIX B: RESPONSE CRITERIA

Lesions should be graded using the following criteria from the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (Scher et al. 2016):

- Soft tissue lesions (lymph node, prostate, visceral)
  - Soft tissue lesions should be assessed for response rate and progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Lymph node target lesions should be recorded by as locoregional or extrapelvic (retroperitoneal, mediastinal, thoracic or other). Existing pathological lymphadenopathy will be defined per RECIST v1.1. Lymph nodes that were previously normal in size must have grown at least 5 mm in the short axis from baseline or nadir and be ≥1 cm in the short access to have progressed.
- Visceral lesions should be designated separately as lung, liver, adrenal, or central nervous system.
- Bone
  - The presence or absence of bone metastases on bone scan will be documented at baseline and lesion number will be documented and assessed serially at each tumor assessment using the bone scan assessment tool.
  - For patients who develop equivocal bone lesions while on study, the use of other scanning modalities, including MRI, positron emission tomography, or other investigational scans that were not used to determine eligibility are discouraged.
  - Progression is defined as at least 2 new lesions; if equivocal, confirm by repeat bone scan 8 weeks later; response is not defined.

The type of progression (growth of existing lesions versus development of new lesions) will be documented separately by site.

The following definitions from RECIST v1.1 (Eisenhauer et al. 2009) should be used:

- Evaluation of Target Lesions
  - Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
  - Partial Response (PR): At least a 30% decrease in the sum of the diameters (SOD) of target lesions, taking as reference the baseline SOD.
  - Progressive Disease: At least a 20% increase in the SOD of target lesions, taking as reference the smallest sum recorded since the treatment started or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The development of unequivocal new lesions (not attributed to differences in scanning technique, imaging modality, or flare/healing of pre-existing lesions) will also be considered progressive disease.

  - Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify as progressive disease, taking as reference the smallest SOD since the treatment started.
- Special Notes on the Assessment of Target Lesions
  - Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD, and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Evaluation of Non-Target Lesions
  - Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.
  - Incomplete Response/Stable Disease (non-CR/non-progressive disease): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
  - Progressive Disease: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
  - Tumor markers alone cannot be used to assess objective tumor response or disease progression. If the PSA is initially above the upper limit, it must normalize for patients to be considered in CR.
- Special Notes on Assessment of Progression of Non-Target Disease
  - To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

APPENDIX C: EXAMPLES OF MEDICATIONS AND FOODS THAT ARE PROHIBITED OR TO BE USED WITH CAUTION

The following medications and foods are examples of prohibited medications/foods or medications/foods to be used with caution during the study:

	Prohibited	Use with Caution
CYP3A4 Inducers	St. John's wort Carbamazepine, phenytoin, rifampin	Bosentan, efavirenz, etravirine, modafinil, nafcillin
CYP3A4 Inhibitors	Grapefruit and Seville oranges (including marmalade and juices made from these fruits) Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil
CYP3A4 Substrates	Alfentanil, aprepitant, astemizole, budesonide, buspirone, cisapride, conivaptan, cyclosporin, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	
CYP2C8 Inducers	Rifampin	
CYP2C8 Inhibitors	Gemfibrozil	Glimepiride, tolbutamide[a]
CYP2C9 Substrates	Celecoxib, phenytoin	Warfarin[b]
CYP2C19 Substrates	S-mephenytoin, omeprazole, lansoprazole, esomeprazole[c], clobazam	
Corticosteroids or GR modulators	Mifepristone or other GR antagonists	Topical or oral corticosteroids
QT-prolonging medications		Substitute or eliminate QT-prolonging medications, when possible (https://www.crediblemeds.org/)

BID, twice daily; CYP, cytochrome P450; GR, glucocorticoid receptor.

a. For patients receiving sulfonylureas, conduct close glucose monitoring to assess for diabetic control.

b. If co-administration of the study regimen with warfarin cannot be avoided, conduct additional international normalized ratio monitoring.

c. Ranitidine 75 mg BID may be used as an alternative to a proton pump inhibitor, with the dose of ranitidine taken 1 hour after CORT125281 administration.

The above is not an exhaustive list. For a more comprehensive list or to review specific medications, see the following links:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm and http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX D: STANDARD DIET

The suggested meal content should consist of approximately 520 Kcal with approximately 30% calories from fat (total grams of fat, approximately 17 grams). The approximate content of the breakfast meal and time and duration of consumption will be recorded in the study records.
A sample meal description is as follows:

Standard American Heart Association Healthy (Low-Fat) Breakfast

1 box cereal (30-40 g)

Skim milk (240 mL)

1 boiled egg

1 slice toast (15 g)

Margarine (10 g)

Total calories, approximately 520 Kcal

APPENDIX E: SUMMARY OF CHANGES

Significant changes in Amendment 5 of the protocol compared with Amendment 4 of the protocol are summarized below with additional details in Table 23. Minor editorial or stylistic changes made for consistency are not summarized and are not shown in the redline version of the amendment.

- Added a double-blind portion (Segment 2) to the Dose-Determination Phase to determine the recommended dose (RD) for CORT125281 administered once daily (QD) under fed conditions.
- Revised the wording for the other portions of the study for clarity, upon addition of Dose-Determination Phase Segment 2:
  - Changed the name for the "Dose-Escalation Phase" to "Dose-Determination Phase" to better capture the intent for this part of the study.
    - Renamed the first portion of the Dose-Determination Phase (the open-label portion) as "Segment 1" now that there are 2 segments in the Dose-Determination Phase.
  - Changed the name for the Expansion Phase cohorts to avoid confusion with Arms A and B in Dose-Determination Phase Segment 2:
    - Renamed "Cohort A" as the Abiraterone (Abi)-Resistant Cohort.
    - Renamed "Cohort B" as the Androgen-Receptor (AR)-Resistant Cohort.
- Updated eligibility criteria to allow patients with metastatic castration-resistant prostate cancer (mCRPC) with rising prostate-specific antigen (PSA).
- Added the 40-mg softgel capsule formulation of CORT125281 and the placebo capsule.
- Revised the text related to the interim safety analyses to reflect that the Data Review Committee (DRC) will evaluate data from Dose-Determination Phase Segment 2 after all patients have completed 3 cycles of treatment in this part of the study.

Table 23 Summary of Changes in Protocol CORT125281-601 Amendment 5

Section	Revision
Global changes made but not shown in the redline version	Updated the table of contents and the lists of tables and figures. Updated all of the table, figure, and section numbers. Incorporated editorial and stylistic changes as appropriate (e.g., corrected typos, added hyphens, defined acronyms). Rearranged footnotes to be in alphabetical order.
Global changes made and shown in the redline version	For the version of the protocol, changed "Amendment 4" to "Amendment 5" and changed the date from 25 July 2018 to 21 February 2020. Updated the signature page for this version. Added references to Dose-Determination Phase Segment 2 throughout the document, to reflect this added study segment. Revised End-of-Study/Early Termination (EOS/ET) to End-of-Treatment (EOT) for clarity. Revised text to clarify that "study drug" refers to CORT125281 and that "study treatment" refers to the combination of CORT125281 and enzalutamide. Removed references to including patient initials in documents (will identify patients by their unique patient identification number, not initials).
Cover Page	Removed the IND number as this is unnecessary for the protocol. Updated the Good Clinical Practice Statement.
Synopsis	Updated text in synopsis to align with changes noted in the following sections of the body of the protocol.
1.2 Therapeutic Hypothesis	Updated the citation for Kach et al. 2017 as this manuscript has been published.
1.3 CORT125281: A Glucocorticoid Receptor Antagonist	Added the international proprietary name (exicorilant).
1.3.1.1 Pharmacology Related to Mode of Action	Added the citation for Korlym prescribing information.
1.3.1.1.2 Cancer Model	Updated Figure 1 to align with the current CORT125281 IB.
1.3.2 Clinical Data	Updated text to reflect that this text reflected the knowledge at the time the study was initiated.
1.3.2.1 Clinical Update	Added this section to provide updated clinical data from recently completed CORT125281 Phase 1 studies.
1.5.1 Design Considerations	Updated this text to align with the current study design.
1.5.2 Rationale for Dose and Dose Regimen Selection	Added rationale for the evaluation of a the alternative CORT125281 dosing strategy (QD, with upward titration from a starting dose of 240 mg to 320 mg as tolerated in Arm A) in Dose-Determination Phase Segment 2.
1.5.3 Rationale for Patient Selection	Revised text to generalize and better reflect the patient population: This population is consistent with the indication for enzalutamide. Patients who have previously received enzalutamide will be allowed to participate ~~in the Expansion Phase~~, as GR antagonism is intended to target one of the mechanisms of resistance to enzalutamide therapy.
1.6 Benefits and Risks	Revised text to reflect the current knowledge about benefits and risks for CORT125281 and enzalutamide.
2.3 Exploratory Objectives	Revised the exploratory objectives:

Section	Revision
	• Evaluate the effects of CORT125281 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 CORT125281 and enzalutamide by line of therapy and in specific sub-sets of disease, including: – GR positive versus GR negative, 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 analyses of exposure-response for measures of efficacy and changes in ~~FK506-binding protein 5 (FKBP5) or other~~ GC-modulated pathways, ACTH/cortisol, or other PD markers • Assess the effect of the pharmacogenomics polymorphisms of the cytochrome P450 pathway on PK and PD parameters **(Dose-Determination Phase Segment 1 only)** • Explore the effects of CORT125281 and enzalutamide **on patient-reported outcomes (PRO) and** quality of life (QoL)
3.1 Overall Design	Revised this section to reflect the addition of the double-blind portion of the Dose-Determination Phase (ie, Segment 2) and to clarify that the open-label portion is now Segment 1 and the Expansion Phase is made up of the Abi-Resistant and ARant-Resistant Cohorts (renamed from Cohorts A and B). Added an updated study design schematic as Figure 2.
3.1.1.1 Dose-Determination Phase Segment 1 (Open-Label)	Added this subsection to organize text in Section 3.1.1. Replaced “dose level” with “cohort”, where appropriate for clarity.
3.1.1.2 Dose-Determination Phase Segment 2 (Double-Blind)	Added this subsection to describe the methodology for Dose-Determination Phase Segment 2.
3.1.2 Expansion Phase **(Phase 2a)**	Revised text to reflect that patients in the Expansion Phase will receive CORT125281 + enzalutamide according to the RD regimen. Renamed Cohorts A and B “Abi-Resistant Cohort” and “ARant-Resistant Cohort” Revised the requirement for the Food-Effect Subcohort (ie, 10 patients, not necessarily the first 10 patients). Added text to clarify that patients who are not in the Food-Effect Subcohort will not have a Lead-In Period.
3.2.1 Number of Patients	Revised this text to reflect the additional patients to be enrolled for evaluation in Dose-Determination Phase Segment 2.
3.3.3 Study Duration	Revised text to clarify that patients will receive combination treatment (CORT125281 + enzalutamide) until they reach a protocol-defined event of disease progression, experience unmanageable toxicity, or until other treatment discontinuation criteria are met.

Section	Revision
4 Study Population	Updated to reflect that patients with mCRPC with rising PSA will be allowed to enroll.
4.1 Inclusion Criteria	Moved the Inclusion Criterion (previously #8, now Inclusion Criterion #4) for progressive disease based on PSA or imaging in Dose-Determination Phase Segment 1 and Expansion Phase. Added the inclusion criterion #5 for Dose-Determination Phase Segment 2: **5. Dose-Determination Phase Segment 2: Currently receiving enzalutamide with a rising PSA as follows:** **a. Rising PSA: 25% increase over nadir and an absolute value of >1 ng/mL by at least 2 measurements obtained ≥1 week apart. PSA measurements can be collected during or after the most recent prior therapy.** **b. Patients must have received enzalutamide for a minimum of 12 weeks and be on stable doses of enzalutamide ≥80 mg QD for at least 4 weeks prior to Cycle 1 Day 1.** • **Patients will continue enzalutamide without interruption during the Screening Period (no wash-out period).** • **This will be the enzalutamide starting dose for combination with CORT125281 beginning on Cycle 1 Day 1.** **c. M0 disease is allowed.** Added requirement for 10 patients to have paired biopsies in Dose-Determination Segment 2 to Inclusion Criterion #10. Updated Inclusion Criterion #11 to clarify the pharmacogenomic sample is only required for patients in the Dose-Determination Phase Segment 1. Updated Inclusion Criterion #13 to reflect that Modification of Diet in Renal Disease (MDRD) will be used to determine creatinine clearance.
4.4 ~~Early~~ Patient Discontinuation **of Treatment or Study Completion**/Withdrawal	Revised heading to better reflect study design, in which patients are treated until reaching a protocol-defined event of disease progression or meeting other treatment discontinuation criteria but should continue in the study for Long-Term Follow-Up assessments.
4.4.1 ~~Early~~ Patient Discontinuation **of Study Treatment**	Revised heading to better reflect study design, in which patients are treated until reaching a protocol-defined event of disease progression or meeting other treatment discontinuation criteria. Added text to clarify that if a patient discontinues CORT125281 they can continue enzalutamide alone. However, if a patient discontinues enzalutamide, CORT125281 will also be discontinued.
4.4.2 ~~Early~~ Patient Withdrawal from Study/**Study Completion**	Revised heading to better reflect study design, in which patients who discontinue treatment should continue in the study for Long-Term Follow-Up assessments.
4.5 Restrictions During the Study	Revised text for clarity, and rearranged text in the last paragraph regarding contraception, to align with the order provided in the inclusion criteria.
5 Study Treatments and Management	Revised text to clarify that the co-administered drug is defined as enzalutamide, and the study treatment is CORT125281 and/or enzalutamide, as administered according to the protocol.
5.1 Study Drug (CORT125281) **and Placebo**	Updated text and Table 1 to reflect the addition of the 40-mg softgel capsule formulation of CORT125281 and the placebo capsule.
5.2 Non-Investigational Medicinal Agent (Enzalutamide)	Updated Table 2 to provide the dose levels for each part of the study.

Section	Revision
5.3 Timing of Study Treatment Administration	Updated text and added subheadings to clarify the timing of study treatment administration in each part of the study (Dose-Determination Phase Segments 1 and 2, and Expansion Phase). Added text to describe the recommended timing for dosing in Dose-Determination Phase Segment 2.
5.4.1 Dose-Determination Phase Segment 1 (Open-Label)	Added section heading and revised text for clarity regarding the evaluation of DLTs in Dose-Determination Phase Segment 1.
5.4.2 Dose-Determination Phase Segment 2 (Double-Blind)	Added section heading and text to describe the DLT-evaluation and dose-determination process in Dose-Determination Phase Segment 2.
5.5. Definition of Dose-Limiting Toxicities	Added text to clarify the DLT-evaluation period: **DLTs will be recorded during the DLT-evaluation period (first dose of CORT125281 through completion of Cycle 1 for Segment 1, and first dose of CORT125281 through completion of Cycle 3 for Segment 2).**
5.6 Maximum Tolerated Dose	Revised text to clarify that the highest dose with a DLT rate of <33% during the DLT-evaluation period will be considered the MTD.
5.7.1 CORT125281 Dose Modification or Delay	Added text to provide recommendations for dose reduction in Dose-Determination Phase Segment 2.
5.7.1.1. Continuation of Enzalutamide After CORT125281 Interruption/Discontinuation	Added this subsection to provide guidance for patients who discontinue CORT125281 but continue on enzalutamide alone.
5.8.1 Intra-Patient Dose Escalation of CORT125281	Added subsection headings to organize text clearly for Dose-Determination Phase Segments 1 and 2. Removed restriction saying CORT125281 and enzalutamide could not be simultaneously escalated.
5.8.1.2 Dose-Determination Phase Segment 2	Added this section to provide guidance on intra-patient dose escalation in Dose-Determination Phase Segment 2.
~~5.8.2 Intra-Patient Dose Escalation of Enzalutamide~~	Removed this section, as it is no longer relevant.
5.9.1 Permitted Concomitant Therapy Requiring Caution	Revised this text to clearly indicate restrictions for concomitant medications as they relate to each study treatment (CORT125281 and/or enzalutamide).
5.9.2 Prohibited Medications/Treatments/ Foods	Added a link to Section 4.2 for wash-out periods for specific medications. Removed cranberry as a restricted food.
5.10 Meals and Dietary Requirements	Added Section 5.10.1 Dose-Determination Phase Segment 2 to reflect that patients should take CORT125281 with their evening meal. Added a subsection heading for the Expansion Phase to clearly organize text.
5.11 Method of Treatment Assignment and Randomization	Added subsection headings to better organize this text and added text for randomization process in Dose-Determination Phase Segment 2.
5.12 Blinding	Added subsection headings to better organize this text as it relates to each part of the study.
5.12.2.1 Unblinding	Added this section and text to cover the unblinding procedures for Dose-Determination Phase Segment 2.
5.14 Product Accountability and Treatment Adherence	Revised text to reflect that accountability will be performed on Day 1 of each cycle and at the EOT Visit.

Section	Revision
6.3.6.1 Laboratory Parameters	Revised text to clarify that the Central Laboratory Manual should be consulted for laboratory procedures. Added serum amylase, serum lipase, spot urine and UFC (both with creatinine) to the list of measurements. Moved thyroid function tests to their own column in the table, for better organization. Moved PSA to "Other" column to align with the organization in the SoA. Revised footnotes in Table 11 for clarity.
6.4 Pharmacodynamic Measures	Revised to align with the current exploratory objectives and endpoints.
6.4.1 Blood Hormones for HPA Axis Effects – 6.4.3 Circulating Tumor Cells	Revised to provide rationale for evaluating the PD endpoints in this study.
6.4.4 Paired Tumor Tissue Biopsies	Revised to reflect the need for 10 patients to have paired biopsies in Dose-Determination Segment 2.
6.4.5 Urinary Free Cortisol and Urine Spot Test	Added this subsection to describe the methods for collecting 24-hour UFC and spot urine tests.
6.6 Pharmacokinetic Measures	Added text for Dose-Determination Phase Segment 2.
6.9 **Patient-Reported Outcomes and** Quality-of-Life Assessments	Revised heading and text to reflect that both PRO and QoL are being evaluated in this study.
7 Study Assessments and Procedures by Study Visit	Revised to align with the current Schedules of Assessments (Appendix A)
8.1.4 Relationship **to Study Treatment**	Revised heading and text in this section to clearly reflect that relationship to both CORT125281 and enzalutamide will be assessed.
8.1.5 Expectedness	Revised text to describe how AE expectedness will be determined.
9.1 General Statistical Considerations	Revised this section to provide methods for analyses for Dose-Determination Phase Segment 2.
9.2 Analysis Populations and Subgroups	Correct definition of Safety Population, as this population will be used for all analyses other than evaluation of DLTs. Revised definition for DLT-Evaluable Population to reflect the addition of Dose-Determination Phase Segment 2.
9.4 Sample Size Calculation	Added subsection headings to clearly organize content for each part of the study. Added text to reflect the sample size in Dose-Determination Segment 2. Added text to reflect the replacement of patients who are not evaluable for DLTs. Revised text for the Expansion Phase to reflect the statistical calculations for the sample size of the Abi-Reistant and ARant-Resistant Cohorts.
9.5.4 Analysis of DLTs	Added text to regarding the analysis of the DLT rate (in patient-weeks).
9.6 Exploratory Analyses	Added text to reflect that additional analysis methods for PRO and QoL assessments will be outlined in the Statistical Analysis Plan.
9.8 ~~Interim Safety Analyses~~ **Data Review Committee** – 9.9 ~~Data Review Committee~~ **Interim Safety Analyses**	Reordered section headings for the Data Review Committee and Interim Safety Analyses and rearranged text to improve clarity regarding the role of the DRC in evaluating data from Dose-Determination Phase Segment 1, Dose-Determination Phase Segment 2, and the Expansion Phase.

Section	Revision
11.4 Long-Term Retention of Biological Samples	Revised text to align with current regulatory guidance on retention of patient samples.
12 References	Updated references to reflect added and updated citations in text.
Appendix A	Revised the Schedules of Assessments in Appendix A to reflect the updated study design and endpoints.
Appendix C	Removed cranberry from the list of prohibited foods. Removed text referring to the morning dose of ranitidine, as it will be restricted any time of day if it is within 1 hour of taking CORT125281.