Official Title: ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined With Enzalutamide or Abiraterone/Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer

NCT Number: NCT03480646

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Clinical Trial Protocol: 1205-201

Study Title: ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer

Study Number: 1205-201

Study Phase: 1b/2

Product Name: CPI-1205

Indication: Metastatic Castration Resistant Prostate Cancer (mCRPC)

Study Sponsor: Constellation Pharmaceuticals, Inc.
215 First Street, Suite 200
Cambridge, MA 02142

Medical Monitor: [redacted], MD
[redacted]
Constellation Pharmaceuticals
Phone: [redacted]
Cell: [redacted]

	Date
Original Protocol (Version 1):	**18 September 2017**
Amendment 1 (Version 1.1):	**21 September 2017**
Amendment 1 (Version 2.0):	**18 October 2017**
Amendment 2 (Version 3.0):	**12 January 2018**
Amendment 3 (Version 4.0):	**26 July 2018**

PRINCIPAL INVESTIGATOR SIGNATURE

I have read the attached Protocol 1205-201, entitled "ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer," dated 26 July 2018. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonization (ICH) Tripartite Guidelines on Good Clinical Practice, effective in the United States from 9 May 1997, and applicable United States Food and Drug Administration (FDA) regulations set forth in 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Constellation Pharmaceuticals.

Principal Investigator - Printed Name	Principal Investigator - Signature	Date

Investigational Site or Name of Institution and Location

[redacted], MD	[redacted]	[redacted]
Medical Monitor - Printed Name	Medical Monitor - Signature	Date

SYNOPSIS

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.	
Name of investigational product: CPI-1205	
Title of study: ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer	
Study Number: 1205-201	
Number of study center(s): Approximately [redacted]	
Study duration • Estimated date first patient enrolled: November 2017 • Estimated date last patient completed for evaluation: Q2 2019	**Phase of development:** Phase 1b/2
Investigational Product: CPI-1205 tablets for oral (PO) administration three times a day (TID) or twice daily (BID) without cobicistat and BID with cobicistat. **Partner Products:** CPI-1205 will be combined with either enzalutamide capsules PO once daily **OR** abiraterone acetate (hereafter referred to as abiraterone) tablets PO once daily. Patients who receive abiraterone will also receive prednisone PO BID (or frequency of prednisone at the discretion of the investigator). As of Amendment 2, new cohort(s) of patients will receive CPI-1205 PO BID along with cobicistat PO BID. **NOTE**: The Study Safety Committee (SSC, see below) may elect to add additional patients to CPI-1205 PO TID cohorts without cobicistat or add PO BID cohorts without cobicistat based on emerging data. Cobicistat dosing will begin with one dose the evening prior to day 1 of CPI-1205 (i.e., the evening of day 0), and then continue PO BID starting on day 1 of CPI-1205. See Section 6.1 for rules regarding drug administration and food. **Control Product(s):** For any randomized phase 2 study, the control arm will be either enzalutamide capsules PO once daily **OR** abiraterone tablets PO once daily plus prednisone PO BID (or frequency of prednisone at the discretion of the investigator). **NOTE:** See Section 6.2.5 for the possibility of BID dosing for abiraterone.	
Objectives: **Phase 1b Dose Escalation: Primary Objective** To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of CPI-1205 + enzalutamide and CPI-1205 + abiraterone/prednisone in patients with metastatic castration resistant prostate cancer (mCRPC). **NOTE:** The MTD will be determined for CPI-1205 PO BID with cobicistat for each combination. The SSC may also elect to determine the MTD for CPI-1205 PO TID, however, only one of the CPI-1205	

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Name of investigational product: CPI-1205

dosing schedules (i.e., either TID or BID with cobicistat) will be selected as the RP2D for each combination.

Phase 1b Dose Escalation: Secondary Objectives

- To characterize the safety and tolerability profile of CPI-1205 (with or without cobicistat) + enzalutamide and CPI-1205 (with or without cobicistat) + abiraterone/prednisone.
- To characterize the pharmacokinetic (PK) profiles of CPI-1205, cobicistat, enzalutamide and abiraterone, and evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.
- To evaluate preliminary signs of efficacy of CPI-1205 (with or without cobicistat) + enzalutamide and CPI-1205 (with or without cobicistat) + abiraterone/prednisone.
- [redacted]

As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population (referred to as heavily pretreated expansion cohort(s) [HPEC(s)]). See Methodology below for additional details on the population to be enrolled and choice of regimen(s) for the HPEC(s).

Phase 1b HPEC(s): Primary Objective

To estimate objective response rate (ORR) as determined by central radiology review (CRR) of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone in the HPEC.

Phase 1b HPEC(s): Secondary Objectives

NOTE: radiographic response and progression are defined per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria.

- To characterize the safety and tolerability profile of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone in the heavily pretreated population.
- To estimate ORR as determined at the site by the investigator.
- To estimate ORR (excluding parenchymal lesions) as determined by CRR.
- To estimate prostate specific antigen (PSA) 50% response rate (PSA50).

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Name of investigational product: CPI-1205

- To estimate time to PSA progression.
- To estimate radiographic progression free survival (rPFS) as determined by CRR and at the site by the investigator.
- To estimate overall survival (OS).
- To estimate duration of response (DOR) as determined by CRR and at the site by the investigator and DOR (excluding parenchymal lesions) as determined by CRR.
- To estimate the time to first skeletal-related event (SRE) and the time to first symptomatic skeletal event (SSE).
- To estimate time to unequivocal clinical progression.
- To estimate time to initiation of new systemic treatment for prostate cancer.
- [redacted]
- To estimate the time to pain progression and the time to opioid analgesics.
- To estimate the circulating tumor cells (CTC) 30% response rate and CTC conversion rate in patients with unfavorable CTCs.
- [redacted]
- To further characterize the PK profiles of CPI-1205, cobicistat (if applicable), enzalutamide or abiraterone, and further evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.

Following determination of the MTD and RP2D during phase 1b dose escalation, one or both of the second generation androgen inhibitor combinations (i.e., CPI-1205 [with or without cobicistat] in combination with either enzalutamide or abiraterone/prednisone) may proceed to phase 2 after consideration of PK, pharmacodynamic results, data from the HPEC(s) and safety data. If the decision is made to proceed to phase 2, the first phase 2 trial will be conducted as a randomized phase 2 trial comparing CPI-1205 (with or without cobicistat) combined with either enzalutamide **OR** abiraterone/prednisone (the combination arm) versus enzalutamide **OR** abiraterone/prednisone (the control arm). If a second phase 2 trial is conducted, it may be a second randomized phase 2 trial, or a single arm trial (decision based on factors such as preliminary efficacy and PK). **NOTE:** phase 2 may begin prior to completing the phase 1b HPEC(s).

Randomized Phase 2: Primary Objective

To evaluate the effect of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone (combination arm) versus (vs) enzalutamide **OR** abiraterone/prednisone alone (control arm) in patients with mCRPC.

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Name of investigational product: CPI-1205

Randomized Phase 2: Secondary Objectives

NOTE: radiographic response and progression are defined per the PCWG3 criteria and may be evaluated by CRR and at the site by the investigator. ORR (excluding parenchymal lesions) and DOR (excluding parenchymal lesions) will only be evaluated by CRR.

NOTE: The combination arm referred to in the objectives below may be with or without cobicistat.

- To compare rPFS and rPFS at 3 months between the combination arm and the control arm.
- To compare time to PSA progression between the combination arm and the control arm.
- To compare ORR and DOR in patients with soft tissue disease between the combination arm and the control arm.
- To compare ORR (excluding parenchymal lesions) and DOR (excluding parenchymal lesions) in patients with non-parenchymal soft tissue disease between the combination arm and the control arm.To compare the composite response rate (where response is defined as PSA 50% response or objective response) in patients with soft tissue disease between the combination arm and the control arm.
- To compare the composite response rate (where response is defined as PSA 50% response or CTC 30% response) in patients with unfavorable CTCs between the combination arm and the control arm.
- To compare the time to first SRE and the time to first SSE between the combination arm and the control arm.
- To compare the time to unequivocal clinical progression between the combination arm and the control arm.
- To compare the time to initiation of new systemic treatment for prostate cancer between the combination arm and the control arm.

[redacted]

- To compare the time to pain progression and the time to opioid analgesics between the combination arm and the control arm.
- To compare the CTC 30% response rate and CTC conversion rate in patients with unfavorable CTCs between the combination arm and the control arm.
- To compare OS between the combination arm and the control arm.

[redacted]

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Name of investigational product: CPI-1205

- To evaluate the safety of CPI-1205 in combination with enzalutamide **OR** abiraterone/prednisone (combination arm).
- In the combination arm(s) only to further characterize the PK profiles of CPI-1205, cobicistat (if applicable), enzalutamide or abiraterone, and further evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.

Single Arm Phase 2: Primary Objective

- To evaluate the effect of the combination selected for the single arm phase 2

Single Arm Phase 2: Secondary Objectives

NOTE: If a single arm phase 2 is conducted, the same endpoints will be evaluated as for the randomized phase 2, but they will be estimated or evaluated for the single arm rather than compared as for the randomized phase 2.

Phase 1b (Dose Escalation and HPEC[s]) and Phase 2 (Randomized and Single Arm):

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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Name of investigational product: CPI-1205

Endpoints:

Phase 1b Dose Escalation: Primary Endpoint

- The MTD will be determined based on the rate of dose-limiting toxicities (DLTs). The RP2D will be selected based on PK and the overall tolerability of the combination, but will not exceed the MTD.

Phase 1b HPEC(s): Primary Endpoint

- ORR is defined as the proportion of patients with a complete response (CR) or partial response (PR) per PCWG3 and as determined by CRR. **NOTE:** all patients in the HPEC(s) must have at least one measurable lymph node at study entry.

Phase 2 (Randomized and Single Arm): Primary Endpoints

The co-primary endpoints include the following:

- PSA50 is defined as the proportion of patients who have a ≥50% reduction in PSA from baseline, after at least 1 dose of study treatment.
- The composite response rate is defined as the proportion of patients who have either a CTC 30% response or an objective response after at least 1 dose of study treatment.
    - CTC 30% response is defined as a ≥30% reduction in CTCs from baseline in patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood).
    - Objective response is defined as a CR or PR per PCWG3 in patients who enter the trial with measurable soft tissue disease. Response will be based on CRR.

NOTE: At least 50% patients in phase 2 must have measurable soft tissue disease at study entry.

Secondary Endpoints

See Section 2.2.4 of the protocol for definition of secondary efficacy endpoints and Section 2.2.5 of the protocol for definition of additional secondary endpoints.

Methodology: Multicenter, open label, phase 1b/2 study of CPI-1205 alone and with cobicistat in combination with enzalutamide or abiraterone/prednisone in patients with a confirmed diagnosis of metastatic adenocarcinoma of the prostate that has progressed in the setting of medical or surgical castration (i.e., mCRPC) and previously treated with a second generation androgen inhibitor.

During phase 1b dose escalation, patients must have been treated with at least one second

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Name of investigational product: CPI-1205

generation androgen inhibitor (prior chemotherapy is also allowed). Prior to Amendment 2, patients were enrolled into phase 1b Dose Level 1A (CPI-1205 PO TID + enzalutamide or abiraterone/ prednisone). The SSC (see below) may elect to add additional patients to this cohort and/or to Dose Level (-)1A, and to determine an MTD for CPI-1205 PO TID. Cohorts of CPI-1205 PO BID may also be explored. As of Amendment 2, additional cohorts will be enrolled: 1) dose escalating CPI-1205 PO BID + fixed dose cobicistat PO BID and enzalutamide and 2) dose escalating CPI-1205 PO BID + fixed dose cobicistat PO BID and abiraterone/prednisone. Within each combination (which will be enrolled simultaneously) successive cohorts will be enrolled at escalating doses of CPI-1205 until the MTD is determined.

The MTD for each combination (and possibly schedule) is defined as the highest dose level at which [redacted] evaluable patients (or [redacted] evaluable patients if a cohort is expanded, see Statistical Considerations below) experience a DLT. The first cycle (defined as 4 weeks) for each combination will be used for purposes of DLT evaluation. **NOTE:** Intra-patient dose escalation of CPI-1205 is not allowed. The RP2D for each combination will be selected based on PK and overall tolerability data (i.e., DLT, cumulative and/or delayed toxicity that limits dosing) from all patients treated at different dose levels in this study and will not exceed the MTD.

As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population. To be included in the HPEC(s), patients must have had prior treatment with and progressed on chemotherapy in the mCRPC setting, and must have been treated with and progressed on two lines of a second generation androgen inhibitor (one from each class; the 2 classes are cytochrome P450 (CYP)17 inhibitors [e.g., abiraterone, orteronel] and AR inhibitors [e.g., enzalutamide, apalutamide]). Patients must also have at least one measurable lymph node. [redacted] A HPEC may begin enrollment if [redacted] atients treated with a specific regimen (i.e., CPI-1205 with or without cobicistat, in combination with enzalutamide or abiraterone) at a given dose level during phase 1b dose escalation experience a DLT. **NOTE:** the SSC will recommend which regimen(s) and dose to evaluate in the HPEC(s) based on safety, PK, efficacy, etc. **NOTE:** a Simon's 2-stage design will be used for any HPEC that opens. After enrollment of [redacted] patients (stage 1), the SSC will recommend whether to continue to stage 2 [redacted] PK,

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Name of investigational product: CPI-1205

efficacy, etc.

Throughout phase 1b (all cohorts), safety oversight will be provided by the SSC comprised of study investigators, the medical monitor (or external medical representative of the Sponsor), and the Sponsor.

Following determination of the MTDs during phase 1b dose escalation, only one of the CPI-1205 dosing schedules will be selected as the RP2D for each combination (i.e., with enzalutamide and with abiraterone/prednisone). One or both of these combinations may proceed to phase 2 after consideration of PK and pharmacodynamic results, data from the HPEC(s) and safety data. **NOTE:** phase 2 may begin prior to the completion of the HPEC(s). During phase 2, enrollment will be limited to patients who have received only one second generation androgen inhibitor (from a different class than the agent chosen for the applicable phase 2 study), who progressed after at least 24 weeks of treatment with the second generation androgen inhibitor, and who have not received prior chemotherapy for mCRPC. In addition, at least 50% of patients enrolled in any phase 2 trial that is opened must have measurable soft tissue disease. [redacted] Patients in the control arm of the randomized phase 2 trial(s) will have the option to cross over to the combination arm at the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE once the decision is made to initiate another systemic treatment for prostate cancer AND provided patients are eligible to participate in the combination arm (see Section 5.5.1).

NOTE: At the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE, patients enrolled in phase 1b Dose Level 1A (CPI-1205 PO TID without cobicistat) may have the option to switch to CPI-1205 PO BID with cobicistat at the discretion of the investigator, and only after consultation with the Medical Monitor. See Section 5.4.9.

Number of Patients (planned): The number of patients in phase 1b dose escalation will depend on safety, but could range from approximately [redacted] (including

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Name of investigational product: CPI-1205

patients from the CPI-1205 TID and CPI-1205 BID with cobicistat cohorts). Approximately [redacted] evaluable patients will be enrolled in any Simon's 2-stage design for any phase 1b HPEC that opens. The number of patients in phase 2 will depend on whether 1 or 2 randomized trials are conducted. Any randomized trial that is opened will enroll approximately [redacted] evaluable patients ([redacted] patients per arm). Any single arm trial will enroll up to [redacted] evaluable patients.

Patients must meet the following criteria for inclusion in phase 1b dose escalation:

1. Age ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix 1)
3. Life expectancy of at least 12 weeks
4. Histologically or cytologically confirmed adenocarcinoma of the prostate. **NOTE**: pure small cell carcinoma is excluded.
5. Documented metastatic disease
6. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue GnRH analog or antagonist (medical castration).
7. Serum testosterone <50 ng/dL
8. Progressive disease in the setting of medical or surgical castration (i.e., CRPC) as assessed by the investigator and that includes at least one of the following:
    a. Evidence of progression as measured by PSA increase of ≥25% and an absolute increase of ≥2 ng/mL in < 6 months from end of last therapy prior to enrollment; **NOTE**: increase should be measured from nadir (in patients with a decline in PSA during last therapy) or baseline (in patients without a decline in PSA during last therapy) **AND/OR**
    b. Soft tissue disease progression as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 **AND/OR**
    c. Bone disease progression defined by two or more new lesions on bone scan
9. Bisphosphonate or denosumab therapy allowed provided dose has been stable for ≥ 4 weeks prior to day 1 of treatment.
10. Prior treatment:
    a. Prior treatment for mCRPC must have included at least one line with a second generation androgen inhibitor (e.g., abiraterone, enzalutamide, apalutamide, daralutamide); **NOTE:** if patient currently on a second generation androgen inhibitor, they must be willing and able to undergo a 2-week washout of the drug prior to day 1 of treatment.
    b. Prior chemotherapy is allowed when administered in the metastatic hormone-sensitive prostate cancer setting. In addition, up to one line of chemotherapy is allowed in the mCRPC setting.

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Name of investigational product: CPI-1205

c. Prior treatment with sipuleucel-T, radium-223, or other non-chemotherapy based treatments for mCRPC (e.g., olaparib, pembrolizumab) is allowed.

11. Recovery from recent surgery, radiotherapy,chemotherapy or other anti-cancer treatment to baseline or ≤ Grade 1 (other than alopecia)
12. Demonstrate adequate organ function as defined below; all screening labs to be obtained within 28 days prior to day 1 of treatment.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1,000/µL
Platelet Count	≥ 100,000/µL (without transfusion support in prior 2 weeks)
Hemoglobin (Hgb)	≥ 8 g/dL (**NOTE:** without transfusion support in the prior month)
Renal	
Serum creatinine **OR** Creatinine clearance (CrCl)	≤ 2 × upper limit of normal (ULN) **OR** ≥ 40 mL/min as estimated by the Cockcroft and Gault formula[1] in subjects with creatinine > 2 × ULN
Hepatic	
Bilirubin	≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 × ULN
Aspartate aminotransferase (AST)	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Alanine aminotransferase (ALT)	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Other	
Serum potassium	Within normal limits (**NOTE**: supplementation to achieve this allowed)
Serum albumin	≥ 3 g/dL
[1]See formula in Appendix 2	

13. Patients who have not undergone a bilateral orchiectomy and have a female partner of childbearing potential must use an adequate barrier method of contraception during study treatment and for 90 days after receiving the last dose of CPI-1205.
14. [redacted]
15. Ability to swallow and retain oral medications

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Name of investigational product: CPI-1205

16. Ability to understand and willingness to sign an IRB approved written informed consent form (ICF) and authorization permitting release of personal health information including genetic testing relevant to cancer.
17. Able to comply with study visit schedule and assessments

Patients who meet any of the following criteria will not be enrolled in phase 1b dose escalation:

1. Known symptomatic brain metastases (**NOTE:** patients with treated epidural disease are allowed)
2. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of treatment (**NOTE**: patients must also meet inclusion criterion #11):
    a. First-generation AR antagonists (e.g., bicalutamide, nilutamide, flutamide) within 4 weeks
    b. 5 alpha reductase inhibitors, ketoconazole, estrogens (including diethylstilbesterol [DES]), or progesterones within 2 weeks
    c. Chemotherapy within 3 weeks
    d. Biologic therapy within 4 weeks
    e. Investigational therapy within 3 weeks (or within a time interval less than at least 5 half-lives of the investigational agent [if known], whichever is longer).
    f. Immunotherapy within 4 weeks
    g. Radionuclide therapy within 4 weeks
3. Radiation therapy for the treatment of metastasis within 1 week prior to day 1 of treatment (**NOTE**: a single fraction of radiotherapy for palliation confined to one field **IS** permitted within 1 week prior to day 1 of treatment)
4. Herbal products that may decrease PSA levels within 4 weeks prior to day 1 of treatment
5. Systemic steroids greater than 10 mg of prednisone/prednisolone per day within 4 weeks prior to day 1 of treatment (**NOTE:** see Section 6.3.2.5)
6. Major surgery within 4 weeks prior to day 1 of treatment
7. Planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery
8. Structurally unstable bone lesions concerning for impending fracture
9. Clinically significant cardiovascular disease including:
    a. Myocardial infarction (MI)/stroke within 6 months prior to day 1 of treatment
    b. Unstable angina within 3 months
    c. Congestive heart failure (CHF) with New York Heart Association (NYHA; see Appendix 3) class 3 or 4
    d. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)

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Name of investigational product: CPI-1205

e. Uncontrolled hypertension (systolic blood pressure (BP) > 170 mmHg or diastolic BP > 105 mmHg at screening) despite two concomitant antihypertensive therapies
f. QT interval corrected by the Fridericia correction formula (QTcF) >500 msec on the screening electrocardiogram (ECG)

10. Active or symptomatic viral hepatitis or chronic liver disease
11. History of unresolved adrenal dysfunction
12. Gastrointestinal (GI) disorder that negatively affects absorption
[redacted]
14. Achlorhydria, either documented or suspected on the basis of an associated disease (e.g., pernicious anemia, atrophic gastritis, or certain gastric surgical procedures)
15. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within 12 months prior to day 1 of treatment, cerebral vascular accident or brain arteriovenous malformation
16. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ bladder cancer, or other cancer for which the patient has been disease-free for at least two years
17. Any other concurrent severe and/or uncontrolled concomitant medical condition that could compromise participation in the study (e.g., clinically significant pulmonary disease, clinically significant psychiatric or neurological disorder, active or uncontrolled infection)
18. Patient unwilling or unable to comply with this study protocol

Patients must meet the following criteria for inclusion in phase 1b HPEC(s):

1. Age ≥ 18 years
2. ECOG performance status 0-1(see Appendix 1); **NOTE**: performance status must be documented by 2 independent evaluators.
3. Life expectancy of at least 12 weeks
4. Histologically or cytologically confirmed adenocarcinoma of the prostate; **NOTE**: pure small cell carcinoma is excluded.
5. Documented metastatic disease.
6. At least one measurable lymph node per PCWG3 (see Section 10.2.1)
7. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue GnRH analog or antagonist (medical castration)
8. Serum testosterone <50 ng/dL
9. Progressive disease in the setting of medical or surgical castration (i.e., CRPC) as assessed by the investigator and that includes at least one of the following:

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Name of investigational product: CPI-1205

a. Evidence of progression as measured by PSA defined as: PSA ≥ 2 ng/mL (or PSA ≥ 1 ng/mL if PSA progression is the only manifestation of progressive disease) and rising PSA by at least 2 consecutive measurements a minimum of 1-week apart **AND/OR**
b. Soft tissue disease progression as per RECIST 1.1 **AND/OR**
c. Bone disease progression defined by two or more new lesions on bone scan

10. Prior treatment:
    a. Prior treatment must have included and patient must have progressed on two lines of a second generation androgen inhibitor, one from each class (i.e., a CYP17 inhibitor [e.g., abiraterone, orteronel] **AND** an AR inhibitor [e.g., enzalutamide, apalutamide]); **NOTE:** if patient currently on a second generation androgen inhibitor, they must be willing and able to undergo a 2-week washout of the drug prior to day 1 of treatment. **NOTE:** if progressive disease is based on PSA, patient must not have evidence of anti-androgen withdrawal syndrome during washout.
    b. The last second generation androgen inhibitor treatment received must not be from the same class as that incorporated in the applicable HPEC; i.e., if the HPEC incorporates enzalutamide, the last second generation androgen inhibitor therapy cannot be enzalutamide, apalutamide, etc.
    c. Prior chemotherapy for mCRPC must have included at least one and no more than two prior lines of taxane-based chemotherapy (**NOTE:** patient must have progressed during at least one line); chemotherapy (including taxane-based) administered in the metastatic hormone-sensitive prostate cancer setting is allowed.
    d. Prior treatment with sipuleucel-T, radium-223, or other non-chemotherapy based treatments for mCRPC (e.g., olaparib, pembrolizumab, nivolumab) is allowed.
11. Recovery from recent surgery, radiotherapy, chemotherapy or other anti-cancer treatment to baseline or ≤ Grade 1 (other than alopecia)
12. Demonstrate adequate organ function as defined in the table below; all Screening labs to be obtained within 28 days prior to day 1 of treatment.

System	Laboratory Value
Hematological	
ANC	≥ 1,000/µL
Platelet Count	≥ 100,000/µL (without transfusion support in prior 2 weeks)
Hgb	≥ 8 g/dL (**NOTE:** without transfusion support in the prior month)
Renal	
Serum creatinine **OR**	≤ 2 × ULN **OR**
CrCl	≥ 40 mL/min as estimated by the Cockcroft and Gault formula[1] in subjects with creatinine > 2 X ULN

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Name of investigational product: CPI-1205

Hepatic	
Bilirubin	≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 x ULN
AST	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
ALT	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Other	
Serum potassium	Within normal limits (**NOTE**: supplementation to achieve this allowed)
Serum albumin	≥ 3 g/dL
[1]See formula in Appendix 2	

13. Patients who have not undergone a bilateral orchiectomy and have a female partner of childbearing potential must use an adequate barrier method of contraception during study treatment and for 90 days after receiving the last dose of CPI-1205.
14. [redacted]
15. Ability to swallow and retain oral medications.
16. Ability to understand and willingness to sign an IRB approved written ICF and authorization permitting release of personal health information including genetic testing relevant to cancer.
17. Able to comply with study visit schedule and assessments.

Patients who meet any of the following criteria will not be enrolled in the phase 1b HPEC(s):

1. Known symptomatic brain metastases (**NOTE:** patients with treated epidural disease are allowed)
2. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of treatment (**NOTE**: patients must also meet inclusion criterion #11):
    a. First generation: AR antagonists (e.g., bicalutamide, nilutamide, flutamide) within 4 weeks
    b. 5 alpha reductase inhibitors, ketoconazole, estrogens (including DES), or progesterones within 2 weeks
    c. Chemotherapy within 3 weeks
    d. Biologic therapy within 4 weeks

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Name of investigational product: CPI-1205

e. Investigational therapy within 3 weeks (or within a time interval less than at least 5 half-lives of the investigational agent [if known], whichever is longer).
f. Immunotherapy within 4 weeks
g. Radionuclide therapy within 4 weeks

3. Radiation therapy for the treatment of metastasis within 1 week prior to day 1 of treatment (**NOTE**: a single fraction of radiotherapy for palliation confined to one field **IS** permitted within 1 week prior to day 1 of treatment)
4. Herbal products that may decrease PSA levels within 4 weeks prior to day 1 of treatment
5. Systemic steroids greater than 10 mg of prednisone/prednisolone per day within 4 weeks prior to day 1 of treatment (**NOTE:** see Section 6.3.2.5)
6. Major surgery within 4 weeks prior to day 1 of treatment
7. Structurally unstable bone lesions concerning for impending fracture
8. Clinically significant cardiovascular disease including:
    a. MI/Stroke within 6 months prior to day 1 of treatment
    b. Uncontrolled angina within 3 months
    c. CHF with NYHA (see Appendix 3) class 3 or 4
    d. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    e. Uncontrolled hypertension (systolic BP > 170 mmHg or diastolic BP > 105 mmHg at screening) despite two concomitant antihypertensive therapies
    f. QTcF >500 msec on the screening ECG
9. Active or symptomatic viral hepatitis or chronic liver disease
10. History of unresolved adrenal dysfunction
11. GI disorder that negatively affects absorption
12. Required treatment with one of the prohibited concomitant medications; **see Section 6.3 and Appendix 4**; **NOTE: each patient's list of concomitant medications MUST be checked against the list of prohibited concomitant medications in Appendix 4.**
13. Achlorhydria, either documented or suspected on the basis of an associated disease (e.g., pernicious anemia, atrophic gastritis, or certain gastric surgical procedures)
14. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within 12 months prior to day 1 of treatment, cerebral vascular accident or brain arteriovenous malformation
15. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ bladder cancer, or other cancer for which the patient has been disease-free for at least two years
16. Any other concurrent severe and/or uncontrolled concomitant medical condition that could compromise participation in the study (e.g., clinically significant pulmonary disease, clinically significant psychiatric or neurological disorder, active or uncontrolled infection)

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Name of investigational product: CPI-1205

17. Patient unwilling or unable to comply with this study protocol

Patients must meet the following criteria for inclusion in phase 2:

1. Age ≥ 18 years
2. ECOG performance status 0-1 (see Appendix 1)
3. Life expectancy of at least 12 weeks
4. Histologically or cytologically confirmed adenocarcinoma of the prostate. **NOTE**: pure small cell carcinoma is excluded.
5. Documented metastatic disease. **NOTE**: at least 50% of patients in each phase 2 trial opened must have measurable disease (see Section 4.3).
6. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue GnRH analog or antagonist (medical castration).
7. Serum testosterone <50 ng/dL
8. Progressive disease in the setting of medical or surgical castration (i.e., CRPC) as assessed by the investigator and that includes at least one of the following:
    a. Evidence of progression as measured by PSA defined as: PSA ≥ 2 ng/mL (or PSA ≥ 1 ng/mL if PSA progression is the only manifestation of progressive disease) and rising PSA by at least 2 consecutive measurements a minimum of 1-week apart **AND/OR**
    b. Soft tissue disease progression as per RECIST 1.1 **AND/OR**
    c. Bone disease progression defined by two or more new lesions on bone scan
9. Bisphosphonate or denosumab therapy allowed provided dose has been stable for ≥ 4 weeks prior to day 1 of treatment.
10. Prior treatment:
    a. Only one prior line of a second generation androgen inhibitor from a different class than the one chosen for the applicable phase 2 study (the 2 classes are CYP17 inhibitors [e.g., abiraterone, orteronel] and AR inhibitors [e.g., enzalutamide, apalutamide]). Patient must have progressed after ≥ 24 weeks of treatment with this second generation angrogen inhibitor. **NOTE:** if patient currently on a second generation androgen inhibitor, they must be willing and able to undergo a 2-week washout of the drug prior to day 1 of treatment. **NOTE:** patient must not have evidence of anti-androgen withdrawal syndrome during washout.
    b. No prior chemotherapy for mCRPC allowed; chemotherapy (including taxane-based) administered in the metastatic hormone-sensitive prostate cancer setting is allowed.
    c. Prior treatment with sipuleucel-T, radium-223, or other non-chemotherapy based treatments approved by the US FDA for the treatment of mCRPC is allowed; prior

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Name of investigational product: CPI-1205

treatment with non-chemotherapy based treatments that are not approved for the treatment of mCRPC (e.g., pembrolizumab, ipilimumab, olaparib) are not allowed.

11. Recovery from recent surgery, radiotherapy, chemotherapy or other anti-cancer treatment to baseline or ≤ Grade 1 (other than alopecia)
12. Demonstrate adequate organ function as defined below; all screening labs to be obtained within 28 days prior to day 1 of treatment.

System	Laboratory Value
Hematological	
ANC	≥ 1,000/µL
Platelet Count	≥ 100,000/µL (without transfusion support in prior 2 weeks)
Hgb	≥ 8 g/dL (**NOTE:** without transfusion support in the prior month)
Renal	
Serum creatinine **OR** CrCl	≤ 2 × ULN **OR** ≥ 40 mL/min as estimated by the Cockcroft and Gault formula[1] in subjects with creatinine > 2 × ULN
Hepatic	
Bilirubin	≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 × ULN
AST	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
ALT	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Other	
Serum potassium	Within normal limits (**NOTE**: supplementation to achieve this allowed)
Serum albumin	≥ 3 g/dL
[1]See formula in Appendix 2	

13. Patients who have not undergone a bilateral orchiectomy and have a female partner of childbearing potential must use an adequate barrier method of contraception during study treatment and for 90 days after receiving the last dose of CPI-1205 (or partner drug in the control arm of any randomized phase 2 trial if the patient does not participate in the crossover).
14. [redacted]

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Name of investigational product: CPI-1205

[redacted]

15. Ability to swallow and retain oral medications.
16. Ability to understand and willingness to sign an IRB approved written ICF and authorization permitting release of personal health information including genetic testing relevant to cancer.
17. Able to comply with study visit schedule and assessments.

Patients who meet any of the following criteria will not be enrolled in phase 2:

1. Known symptomatic brain metastases (**NOTE:** patients with treated epidural disease are allowed)
2. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of treatment (**NOTE**: patients must also meet inclusion criterion #11):
    a. First-generation AR antagonists (e.g., bicalutamide, nilutamide, flutamide) within 4 weeks
    b. 5 alpha reductase inhibitors, ketoconazole, estrogens (including DES), or progesterones within 2 weeks
    c. Chemotherapy within 3 weeks
    d. Biologic therapy within 4 weeks
    e. Radionuclide therapy within 4 weeks
3. Radiation therapy for the treatment of metastasis within 1 week prior to day 1 of treatment (**NOTE**: a single fraction of radiotherapy for palliation confined to one field **IS** permitted within 1 week prior to day 1 of treatment)
4. Herbal products that may decrease PSA levels within 4 weeks prior to day 1 of treatment
5. Systemic steroids greater than 10 mg of prednisone/prednisolone per day within 4 weeks prior to day 1 of treatment (**NOTE:** see Section 6.3.2.5)
6. Major surgery within 4 weeks prior to day 1 of treatment
7. Planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery
8. Structurally unstable bone lesions concerning for impending fracture
9. Clinically significant cardiovascular disease including:
    a. MI/stroke within 6 months prior to day 1 of treatment
    b. Unstable angina within 3 months
    c. CHF with NYHA (see Appendix 3) class 3 or 4
    d. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

e. Uncontrolled hypertension (systolic BP > 170 mmHg or diastolic BP > 105 mmHg at screening) despite two concomitant antihypertensive therapies
f. QTcF >500 msec on the screening ECG

10. Active or symptomatic viral hepatitis or chronic liver disease
11. History of unresolved adrenal dysfunction
12. GI disorder that negatively affects absorption
13. [redacted]
14. Achlorhydria, either documented or suspected on the basis of an associated disease (e.g., pernicious anemia, atrophic gastritis, or certain gastric surgical procedures)
15. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within 12 months prior to day 1 of treatment, cerebral vascular accident or brain arteriovenous malformation
16. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ bladder cancer, or other cancer for which the patient has been disease-free for at least two years
17. Any other concurrent severe and/or uncontrolled concomitant medical condition that could compromise participation in the study (e.g., clinically significant pulmonary disease, clinically significant psychiatric or neurological disorder, active or uncontrolled infection)
18. Patient unwilling or unable to comply with this study protocol

Study Treatments:

Investigational agent: CPI-1205 will be supplied as [redacted] tablets to be administered orally. During phase 1b dose escalation, CPI-1205 will be given PO TID without cobicistat, or, as of Amendment 2, CPI-1205 will be given PO BID combined with fixed dose cobicistat PO BID. CPI-1205 PO BID without cobicistat may also be explored. CPI-1205 (with or without cobicistat) will be combined with either enzalutamide or abiraterone/prednisone (see table below for dose levels).

In the phase 1b HPEC(s), CPI-1205 may be given with or without cobicistat in combination with enzalutamide or abiraterone with the specific regimen(s) and dose chosen based on data from the phase 1b dose escalating cohorts. **NOTE**: the SSC will recommend which regimen(s) and dose to evaluate in the HPEC(s) based on safety, PK, efficacy, etc. observed during the phase 1b escalation.

During phase 2, CPI-1205 (with or without cobicistat) will be dosed PO at the RP2D.

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

Dose levels for CPI-1205 (with and without Cobicistat) during phase 1b dose escalation:

[redacted]

Dose/Schedule for enzalutamide during phase 1b (dose escalating cohorts and, if applicable, HPEC) and phase 2 (if applicable): 160mg PO once daily administered as 4 x 40mg capsules as per enzalutamide prescribing information for treatment of mCRPC.*
Dose/Schedule for abiraterone during phase 1b (dose escalating cohorts and, if applicable, HPEC) and phase 2 (if applicable): 1000mg PO once daily administered as 4 x 250mg tablets as per abiraterone prescribing information for treatment of mCRPC.*
Dose/Schedule for prednisone to be given with abiraterone: 5mg PO BID (or frequency of prednisone at the discretion of the investigator).

[redacted]

Rules regarding administration of each agent with or without food are outlined in Section 6.1. In addition, classes of concomitant drugs that are prohibited or to be used with caution are outlined in Section 6.3.

Duration of treatment: In both the phase 1b (all cohorts) and phase 2 portions, 4 week cycles will be repeated until unequivocal clinical progression, radiographic disease progression (as

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.
Name of investigational product: CPI-1205
determined by the investigator) or SRE **AND** planned initiation of other systemic treatment for prostate cancer or until unacceptable toxicity. When this happens to patients in the control arm of any randomized phase 2 trial conducted, patients will have the option to cross over to the combination arm (i.e., continue on the second generation androgen inhibitor and add CPI-1205 [with or without cobicistat] if eligible; see Section 5.5.1). Treatment will continue until unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE **AND** planned initiation of other systemic treatment for prostate cancer or until unacceptable toxicity. **NOTE:** PSA rise without evidence of unequivocal clinical or radiographic progression or PSA rise without a SRE will not be used as a criterion to stop study treatment. Patients who discontinue study treatment for reasons other than radiographic progression will continue to have their disease evaluated by PSA, computed tomography (CT)/magnetic resonance imaging (MRI),bone scan and CTC enumeration* until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. *If study treatment is discontinued prior to the last scheduled CTC collection. Palliative radiation therapy to bone and initiation of bisphosphonates or other approved bone targeting agents are allowed and should not result in discontinuation of study drug therapy. Patients who have not undergone surgical castration must continue their medical castration, i.e., GnRH analog or antagonist, for the duration of study treatment.
Criteria for evaluation: **Dose Limiting Toxicities:** A DLT is defined as an adverse event (AE) or abnormal laboratory value that meets any of the criteria listed in Section 5.4.6 and where a relationship to the investigational agent (CPI-1205 when administered alone or when given with cobicistat) cannot be ruled out. Toxicities will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03). For the purpose of making dose escalation decisions, all DLTs occurring during the first cycle of treatment with CPI-1205 must be included. **Safety:** Throughout the study, safety will be assessed by the recording of AEs, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead ECGs. During phase 1b (all cohorts), safety oversight will be provided by the SSC. The SSC will: • Review all relevant safety findings including DLTs; • During phase 1b dose escalation, determine all cohort dose escalation, dose expansion and de-escalation decisions;

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

- Recommend the regimen(s) and dose to evaluate in phase 1b HPEC(s);
- Recommend whether a CPI-1205 schedule change is warranted after the first stage in phase 1b HPEC(s);
- Determine what additional action is required for AEs that that would qualify as a DLT but occur after 28 days;
- Recommend the RP2D to be used during phase 2

Pharmacokinetics: Serial peripheral blood samples will be drawn before and after dosing in order to determine circulating concentrations of CPI-1205, cobicistat, enzalutamide and abiraterone. PK blood sampling will be required for all patients enrolled in phase 1b dose escalation. During phase 1b dose escalation, serial peripheral blood sampling for PK will occur before and over the 24 hours following dosing on cycle (C) 1 day (D) 1, C1D15, C2D1 and C4D1. In addition, a blood sample for PK will occur prior to dosing on C1D8 and C1D22. For patients receiving CPI-1205 + enzalutamide, serial PK sampling will also occur before and over the 24 hours following dosing on C2D15. From consenting* patients enrolled in a phase 1b HPEC, a blood sample for PK will occur prior to dosing on C1D1, C1D15, and C3D1. In addition, serial peripheral blood sampling for PK will occur before and over the 24 hours following dosing on C2D1. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide, serial PK sampling will also occur before and over the 24 hours following dosing on C2D15. [redacted]

During phase 2 and in the <u>combination arm(s) only</u>, a blood sample for PK will occur prior to dosing on C1D1, C1D15 and C3D1. In addition, serial peripheral blood sampling for PK will occur before and over the 24 hours following dosing on C2D1. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide, serial PK sampling will also occur before and over the 24 hours following dosing on C2D15. **NOTE:** This same schedule will be followed for patients in a randomized phase 2 control arm who participate in the crossover. **NOTE:** An additional PK blood sample is required for any patient who undergoes a dose increase of enzalutamide and/or abiraterone (see Sections 6.2.3 and 6.2.5).

Disease Evaluation: Disease will be evaluated by enumeration of CTCs ([redacted]), PSA, radiographic imaging (including CT/MRI and bone scans) and assessment of pain/usage of opioids. Patients will also be followed for SREs, SSEs, and unequivocal clinical progression. For the phase 1b HPEC(s) and phase 2, sites will be required to submit all radiographic imaging for CRR. **NOTE**: details

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

on the CRR will be provided in a CRR charter, provided as a document separate from the protocol.

In all patients, CTCs will be measured at Screening, on C2D1, C3D1, C4D1, C7D1 and at the End of Treatment Visit. **NOTE:** Changes in CTCs indicative of a 30% response or of a conversion from unfavorable to favorable status must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response or conversion are first met. In all patients, PSA will be measured at Screening, on D1 of each cycle and at the End of Treatment Visit. **NOTE:** Changes in PSA indicative of a PSA 50% response must be confirmed by a second PSA value 4 or more weeks later. In all patients, a CT scan (with contrast) of the chest, abdomen and pelvis, and a bone scan will be performed during Screening, every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) until radiographic progression (as determined by the investigator). Imaging will also be repeated at the End of Treatment Visit. **NOTE:** Changes in tumor measurements indicative of a response must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, assessments will remain on schedule. **NOTE:** For those intolerant of contrast, a cross-sectional MRI scan of the abdomen and pelvis, with a noncontrast CT scan of the chest, may be considered. In all patients, SREs and SSEs will be captured via serial imaging, and via monitoring for clinical pathologic fractures, spinal cord compression, and surgery or radiation therapy to bone. Pain/analgesic use will be evaluated on D1 of each cycle, and at the End of Treatment and Safety Follow-up Visits. **NOTE:** This same schedule will be followed starting Cycle 1 of the combination for patients in a randomized phase 2 who participate in the crossover.

Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2), and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their disease evaluated by PSA, CT/MRI bone scan and CTC enumeration (if study treatment is discontinued prior to the last scheduled CTC collection). PSA and CTCs will be measured and imaging will be performed at the End of Treatment Visit. Subsequent imaging and CTC enumeration should follow the same schedule as if patient had continued on treatment until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. After the End of Treatment Visit, PSA

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Name of investigational product: CPI-1205

should be measured each time imaging is performed.

[redacted]

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Name of investigational product: CPI-1205

[redacted]

Study Treatment Discontinuation: Patients may be discontinued from study treatment and followed up per protocol under the following circumstances if any of the following occur:

- Radiographic disease progression (as determined by the investigator) or unequivocal clinical progression or SRE **AND** planned initiation of other systemic treatment for prostate cancer; **NOTE:** When this happens to patients in the control arm of any randomized phase 2 trial conducted, patients will have the option cross over to the combination arm, provided they are eligible (see Section 5.5.1).
- The treating physician thinks a change of therapy would be in the best interest of the patient
- The patient requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons

End of Treatment Visit: All patients will have an End of Treatment Visit ≤ 7 days after the last dose of CPI-1205 or partner drug in the control arm of any randomized phase 2 trial if the patient does not participate in the crossover. If the patient had all the end of treatment assessments completed ≤ 7 days prior to the last dose, these assessments do not need to be

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.
Name of investigational product: CPI-1205
repeated at the End of Treatment Visit. **NOTE:** CT/MRI and bone scan do not need to be repeated if completed ≤ 28 days prior to the last dose.
Safety Follow-up Visit: All patients who are alive and not lost to follow-up will have a Safety Follow-up Visit 30 days (± 10 days) after the last dose of CPI-1205 or partner drug in the control arm of any randomized phase 2 trial if the patient does not participate in the crossover (**NOTE:** if patient does cross over, then the Safety Follow-up Visit should take place 30 days (± 10 days) after the last dose of CPI-1205). No long-term survival follow-up is required per protocol for phase 1b dose escalation.
Long Term Survival Follow-up (Phase 1b HPEC[s] and Phase 2): In the phase 1b HPEC(s), after the Safety Follow-up Visit, patients will be followed every 3 months until death or the study is closed to collect survival status. In phase 2, after the Safety Follow-up Visit, patients will be followed every 3 months for 2 years and then every 6 months until death or the study is closed to collect survival status.
Withdrawal of patients from the study: Patients will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their subsequent medical care. Additionally, the Sponsor may choose to terminate the study. The investigator also has the right to withdraw patients from the study for any of the following reasons: • Patient withdrew consent • Refusal of treatment/patient request • Protocol violation • Lack of compliance or excessive deviations • Lost to follow-up (after repeated attempts for >30 days have been made to contact the patient including letters sent by registered mail to the patient and designated alternate contact) • Administrative reasons • Intercurrent illness • Death
Statistical Considerations: The number of patients in phase 1b dose escalation will depend on safety, but could range from approximately 15 to 36 per combination (including patients from the CPI-1205 TID and CPI-1205 BID with cobicistat cohorts). Approximately 30 evaluable patients will be enrolled in any Simon's 2-stage design for any phase 1b HPEC that opens. The number of patients in phase 2 will depend on whether 1 or 2 randomized trials are conducted. Anyrandomized trial

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

that is opened will enroll approximately 70 evaluable patients (35 patients per arm). Any single arm trial will enroll up to 29 evaluable patients.

Phase 1b Dose Escalation:

Prior to Amendment 2, patients were enrolled into phase 1b Dose Level 1A. As of Amendment 2, it is anticipated that all new patients will be enrolled into the CPI-1205 PO BID with cobicistat cohorts. However, based on emerging data from these cohorts, the SSC may elect to enroll additional new patients into the TID cohorts (without cobicistat). In addition, the SSC may elect to enroll cohorts to explore 800mg CPI-1205 PO BID (without cobicistat) before selecting the RP2D. This decision will be based on emerging safety, PK, pharmacodynamic and efficacy data from all cohorts.

Dose Level 1A and (-)1A cohorts, i.e., CPI-1205 PO TID without cobicistat:

For each combination the following rules apply (if at least 6 patients are enrolled in Dose Level 1A):

The first patients will be enrolled into the Dose Level 1A cohort.

- If no more than one patient experiences a DLT among six evaluable patients in the Dose Level 1A cohort, this cohort will be considered safe.
- If two patients experience a DLT among six evaluable patients in the Dose Level 1A cohort, the SSC may elect to accrue [redacted] more patients at the same dose level. Alternatively, [redacted] patients may be enrolled in the Dose Level (-)1A cohort.
- If more than two patients experience a DLT among six evaluable patients in the Dose Level 1A cohort, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded. Six patients may be enrolled in the Dose Level (-)1A cohort.

Dose Level 1B, 2B and (-)1B cohorts, i.e., CPI-1205 PO BID with cobicistat:

The dose escalation within each combination will proceed as follows:

The first [redacted] patients will be enrolled in the Dose Level 1B cohort.

- If [redacted] evaluable patients in the Dose Level 1B cohort experiences a DLT, the next [redacted] patients will be assigned to the Dose Level 2B* cohort.

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

- If [redacted] evaluable patients in the Dose Level 1B cohort experiences a DLT, then 3 additional patients will be enrolled at the same dose level.
    - If 0 of the additional patients (i.e., [redacted] evaluable patients in the Dose Level 1B cohort) experiences a DLT, the next [redacted] atients will be assigned to the Dose Level 2B* cohort.
    - If [redacted] of the additional patients (i.e., [redacted] evaluable patients in the Dose Level 1B cohort) experiences a DLT, the MTD will have been exceeded and the next [redacted] patients will be enrolled into the Dose Level (-)1B cohort.
- If [redacted] evaluable patients in the Dose Level 1B cohort experiences a DLT, the MTD will have been exceeded and the next [redacted] patients will be enrolled into the Dose Level (-)1B cohort.

* The dose of CPI-1205 ([redacted]) will be determined based on results from the Dose Level 1B cohort in consultation with the SSC.If the Dose Level 2B cohort opens:

- If [redacted] evaluable patients in the Dose Level 2B cohort experiences a DLT, this cohort will be considered safe.
- If [redacted] evaluable patients in the Dose Level 2B cohort experiences a DLT, then [redacted] additional patients will be enrolled at the same dose level.
    - If [redacted] of the additional patients (i.e., [redacted] evaluable patients in the Dose Level 2B cohort) experiences a DLT, this cohort will be considered safe.
    - If [redacted] of the additional patients (i.e., ≥ [redacted] evaluable patients in the Dose Level 2B cohort) experiences a DLT, the MTD will have been exceeded and additional patients may be enrolled into the Dose Level 1B cohort* (unless [redacted] patients have already been enrolled).
- If [redacted] evaluable patients experience a DLT, the MTD will have been exceeded and additional patients may be enrolled into the Dose Level 1B cohort* (unless [redacted] patients have already been enrolled).

[redacted]

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

NOTE: Dose escalation beyond Dose Level 2B is not allowed.

NOTE: The SSC may elect to add additional patients to any cohort with [redacted] patients with a DLT (or [redacted] patients with a DLT if the cohort has been expanded) to further characterize PK, etc.

The MTD for each combination (and possibly schedule) is defined as the highest dose level at which [redacted] evaluable patients (or [redacted] evaluable patients if a cohort is expanded to [redacted]) experience a DLT. The MTD will not be determined until all patients entered into the cohort under evaluation have either completed Cycle 1 or experienced a DLT. The RP2D for each combination will be selected based on PK and overall tolerability data (i.e., DLT, cumulative and/or delayed toxicity that limits dosing) from all patients treated at different dose levels in this study and will not exceed the MTD. Only one of the CPI-1205 dosing schedules will be selected as the RP2D for each combination.

Phase 1b HPEC(s):

As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population. [redacted]

NOTE: the SSC will recommend which regimen(s) and dose to evaluate in the HPEC(s) based on safety, PK, efficacy, etc.

The primary objective in the HPEC(s) is to estimate the ORR as determined by CRR. [redacted]

Phase 2:

If only one partner product is chosen for phase 2, the phase 2 study will proceed as an open-

Name of Sponsor/company: CONSTELLATION PHARMACEUTICALS, INC.

Name of investigational product: CPI-1205

label randomized phase 2 trial. If both partner products are chosen for phase 2, the second phase 2 trial will be either a second open-label randomized trial, or a single arm phase 2 (following a Simon's 2-stage design). The design of the second trial will be determined by the Sponsor, and will be based on factors such as preliminary efficacy and PK.

Randomized Phase 2:

The primary objective of the randomized phase 2 trial(s) is to evaluate the effect of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone (combination arm) vs enzalutamide **OR** abiraterone/prednisone alone (control arm). [redacted]

Single Arm Phase 2:

A Simon's 2-stage design will be utilized if a single arm phase 2 trial is conducted [redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotrophic hormone
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Androgen receptor
AR-V	Androgen receptor splice variant
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
BP	Blood pressure
BRCA	BReast CAncer genes
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CD	Compact disc
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CL	Total body clearance
Clint	Intrinsic clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CNV	Copy number variations
CPI	Constellation Pharmaceuticals, Inc.
CPK	Creatine phosphokinase
CPRC	Castration Resistant Prostate Cancer
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract Research Organization
CRR	Central radiology review
CT	Computed tomography
CTCs	Circulating tumor cells

CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	[redacted]
C_{trough}	Minimum (trough) concentration
CYP	Cytochrome P450
D	Day
DDI	Drug drug interactions
DES	Diethylstilbesterol
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DKO	Double knock out
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EZH2	Enhancer of Zeste Homolog 2
F	Bioavailability or fraction absorbed
[redacted]	[redacted]
FDA	Food and Drug Administration
[redacted]	[redacted]
FL	Follicular lymphoma
FSH	Follicle-stimulating hormone
GCB-DLBCL	Germinal center B-cell–like diffuse large B cell lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocytic colony stimulating factor
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocytic/monocytic colony stimulating factor
[redacted]	[redacted]
GnRH	Gonadotropin-releasing hormone

[redacted]	[redacted]
H2	Histamine 2 receptor
H3K27me3	trimethylation of lysine 27 of histone 3
[redacted]	[redacted]
[redacted]	[redacted]
Hgb	Hemoglobin
HNSTD	Highest non-severely toxic dose
HPEC	Heavily pretreated expansion cohort
[redacted]	[redacted]
HRD	Homologous Recombination Deficiency
5-HT3	5-hydroxytryptamine
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLN	Less than institutional limits or normal
LVEF	Left ventricular ejection fraction
mCRPC	Metastatic Castration Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NF-kB	Nuclear factor-kappa B

NRS	Numerical rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PARP	Poly ADP ribose polymerase
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic(s)
PO	Orally; by mouth
PR	Partial response
PRBC	Packed red blood cells
PRC2	Polycomb repressive complex 2
PRES	Posterior reversible encephalopathy syndrome
[redacted]	[redacted]
[redacted]	[redacted]
PSA	Prostate specific antigen
PSA50	PSA 50% response rate
PT	Prothrombin time
[redacted]	[redacted]
QTc	QT interval corrected
QTcF	QT interval corrected by the Fridericia correction formula
RB1	Retinoblastoma 1
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
rPFS	Radiographic progression free survival
SAEs	Serious adverse events
SAM	S-adenosylmethionine
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SD	Stable disease
SDD	Spray dried dispersion
SHBG	Sex hormone-binding globulin

siRNA	Small interfering RNA
SRE	Skeletal-related event
SSC	Study safety committee
SSE	Symptomatic skeletal event
[redacted]	[redacted]
SUSARs	Suspected unexpected serious adverse reactions
TDI	Time dependent inhibition
TEN	Toxic epidermal necrosis
$T_{1/2}$	Elimination half-life
T_{max}	Time to maximum concentration
TID	Three times daily
TKO	Triple knock out
TRAEs	Treatment related adverse events
ULN	Upper limit of normal
US	United States
VD_{ss}	Volume of distribution at steady-state
VS	Versus
WBC	White blood cell
WHO	World Health Organization
WNL	Within institutional normal limits

1 INTRODUCTION

1.1 Metastatic Castration Resistant Prostate Cancer

Other than skin cancer, prostate cancer represents the most common cancer in males, with an estimated incidence of just over 160,000 new cases in 2017 in the United States (US), and approximately 27,000 deaths [1]. The large majority of men (92%) present with localized disease and are eligible for cure [1], while a small percentage present with metastatic disease [2]. Unfortunately, approximately 30-50% of patients with localized disease experience a recurrence after potentially curative local treatment, dependent on a number of patient specific risk factors, e.g., level of serum prostate specific antigen (PSA) at diagnosis [3]. Recurrence of disease can manifest solely as an increase in serum PSA (referred to as a biochemical recurrence) or with the development of overt metastatic disease. Of note, the prevalence of measurable soft tissue disease in men with metastatic castration-resistant prostate cancer (mCRPC) enrolled in phase 3 clinical trials after the year 2000 is approximately 50% [4], but is likely less than this in population of all mCRPC patients.

Prostate cancer is dependent on androgens and the androgen receptor (AR) signaling pathway for growth and proliferation [5], at least initially [6], and androgen deprivation therapy (ADT) remains the backbone of the treatment of recurrent or metastatic disease, as initially established in the 1940s [5]. Treatment options for biochemical recurrence only or metastatic disease are the same, although initiation of therapy in the former group may be delayed [7]. ADT is used to achieve castration via surgical (defined as serum testosterone <20 ng/dL) or medical (defined as serum testosterone <50 ng/dL) therapy [6]. Medical therapy is far more commonly used, and involves gonadotropin-releasing hormone (GnRH) agonists or antagonists, alone or in combination with first generation anti-androgens, such as bicalutamide or flutamide [8].

Although responses (including tumor regression, relief of symptoms and reductions in serum PSA) are achieved in ~80% of men with metastatic prostate cancer treated with ADT [9], progression to castration-resistant prostate cancer (CRPC; defined as an increase in PSA, new metastases or progression of existing metastases in the face of castration) is inevitable [8]. CRPC is also associated with significant morbidity, as more than 90% of patients eventually develop metastases in the bone [10] which can lead to significant pain, an increased risk of fracture and anemia. Additional treatment is needed at this point, although ADT is continued as the backbone when CRPC develops, in order to maintain the castrate state [11].

Prior to 2010, the treatment options for CRPC were limited to chemotherapy or additional endocrine therapies. Docetaxel plus prednisone became the standard chemotherapy regimen of choice after a 2004 randomized trial revealed significant survival benefits for this regimen in mCRPC, as compared to the historical standard of mitoxantrone plus prednisone (19.2 versus [vs] 16.3 months) [12, 13]. The most commonly employed endocrine option was the addition of a first generation anti-androgen (if not previously used) to ADT. These are usually used before chemotherapy, in an attempt to control disease and delay chemotherapy related side effects. Responses (usually reductions in serum PSA) are of short duration, and no clear survival benefit has ever clearly been established despite decades of studies evaluating this class of drugs dating back to the 1980s [14, 15]. Based largely on this lack of survival benefit, most clinicians and

researchers believed additional efforts to suppress the AR beyond castration would prove fruitless [15].

In 2010, the dendritic cell vaccine sipuleucel-T was approved by the Food and Drug Administration (FDA) after demonstrating a survival benefit compared to placebo (25.8 vs 21.7 months, p=0.03) in mCRPC patients who are asymptomatic or minimally symptomatic and without visceral metastases [16]. No improvement was seen in time to disease progression, therefore, sipuleucel-T is limited to select patients, i.e., those with slowly progressing disease who are not on steroids or receiving opioids for pain [14].

Since 2011, two new therapies (see Section 1.1.1) have become available that demonstrated a benefit in progression free survival (PFS), overall survival (OS) and quality of life (QOL) vs placebo in randomized phase 3 trials when added to ADT. These include the second generation anti-androgens abiraterone acetate [17, 18] and enzalutamide [19, 20]. Both of these treatments are of benefit either prior to or after docetaxel [21]; see Sections 1.1.1.1 and 1.1.1.2. A third new treatment, the radiopharmaceutical radium 223, also demonstrated significant improvements in OS and QOL vs placebo in the mCRPC population without visceral metastases when dosed monthly for 6 weeks. Based on this study, it was approved by the FDA in 2013 for the treatment of mCRPC patients with symptomatic bone metastases with no known visceral metastases. [22].

Since docetaxel and prednisone is associated with a higher risk of toxicity as compared to these 3 newest treatments [21], chemotherapy is now generally reserved for use in rapidly progressing and/or symptomatic disease [14], or after failure on abiraterone, enzalutamide or radium 223. After progression on docetaxel, the taxane cabazitaxel demonstrated a survival benefit when compared to mitoxantrone plus prednisone. However, it is also associated with significant toxicity, particularly myelosuppression [23].

The optimal sequence of these various options is unknown [11]. The issue of sequencing and whether any of these agents can or should be combined is currently a focus of research [24]. A number of other therapies are also under active investigation for the treatment of mCRPC including (but not limited to) the immunotherapy drug pembrolizumab and poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib). Of the newer approved agents, abiraterone and enzalutamide have the broadest application and are used frequently in the treatment of mCRPC.

Of note, the second generation androgen inhibitors are now proving effective when moved up earlier in the treatment of prostate cancer. Abiraterone was approved by the FDA in February 2018 for the treatment of metastatic high-risk castration sensitive prostate cancer based on significant improvements seen as compared to placebo in OS (median not reached vs 34.7 months; p<0.001) and radiographic PFS (33 months vs 14.8 months; p<0.002) [25]. Apalutamide was approved by the FDA in February 2018 for the treatment of non-metastatic CRPC based on a significant improvement in metastasis-free survival as compared to placebo (40.51 months vs 16.20 months; p<0.0001) [26]. In July 2018, enzalutamide was also approved for the treatment of non-metastatic CRPC based on a significant improvement in metastasis-free survival as compared to placebo (36.6 months vs 14.7 months; p<0.0001) [27]. These new indications mean prior history of treatment with a second generation androgen inhibitor in an earlier prostate cancer setting must be considered when evaluating treatment options for mCRPC.

1.1.1 Second Generation Androgen Inhibition

While typical ADT removes 80% of circulating testosterone, it does not impact the circulating testosterone arising from adrenal steroids [28]. In addition, preclinical studies suggest that prostate tumors may also contribute to the synthesis of extragonadal testosterone [29, 30]. The critical role these extragonadal sources of testosterone play in prostate cancer is evidenced by the success of the second generation androgen inhibitors described below.

1.1.1.1 Abiraterone

Abiraterone acetate (an oral pro-drug of abiraterone, and hereafter referred to as abiraterone) was approved by the FDA for the treatment of mCRPC in 2011. Abiraterone selectively inhibits cytochrome P450 (CYP)17, an enzyme involved in the synthesis of testosterone. Via this mechanism, abiraterone blocks the production of testosterone in the adrenal glands, testes and within the prostate tumor [17]. By inhibiting CYP17, abiraterone also reduces the synthesis of cortisol. Abiraterone is thus always combined with low dose prednisone to mitigate the compensatory increase in adrenocorticotrophic hormone (ACTH) and subsequent accumulation of mineralocorticoid steroids associated with cortisol inhibition. **NOTE:** Since the approval of abiraterone in combination with prednisone 5mg twice daily, studies have been conducted evaluating abiraterone in combination with prednisone 5mg once daily. Investigators have concluded that abiraterone can be safely administered with prednisone at the reduced frequency [31, 32].

The first randomized phase 3 trial of abiraterone plus prednisone was conducted in men who progressed after docetaxel, and demonstrated a significant improvement in both PFS and OS as compared to placebo plus prednisone (5.6 vs 3.6 months; $p<0.0001$ and 15.8 vs 11.2 months; $p<0.0001$, respectively)[18]. In addition to these endpoints, circulating tumor cells (CTCs) were also measured at baseline and serially across the trial (see Sections 1.1.1.3 and 1.4.2 for additional information on CTCs and the association between CTC status and OS). One research area of interest related to CTCs is conversion from an unfavorable ($\geq$ 5 cells/7.5mLs of blood) to favorable ($\leq$ 4 cells/7.5mLs) status after treatment. In this phase 3 trial, across the 2 arms 28% of the 441 evaluable patients for this endpoint converted after 13 weeks of treatment [33]. Another area of interest is a decline of at least 30% in CTCs from baseline in patients with an unfavorable CTC status. In the phase 3 trial, across the 2 arms 42% of the 441 evaluable patients for this endpoint had a decline in CTCs of at least 30% after 13 weeks of treatment [33]. When considering only patients enrolled in the abiraterone/prednisone arm, 73% of patients had a decline in CTCs of at least 30% [34].

A subsequent phase 3 randomized trial also demonstrated significant PFS and OS benefits when abiraterone plus prednisone was compared to placebo plus prednisone in chemotherapy-naïve men with asymptomatic or mildly symptomatic mCRPC (16.5 vs 8.3 months; $p<0.001$ and 34.7 vs 30.3 months; $p=0.0033$, respectively) [35, 36]. The benefit in OS associated with abiraterone was seen despite the frequent use of subsequent therapies such as cabazitaxel and enzalutamide (neither of which was available at the start of this trial) at the time of disease progression.

See Section 9.4.2 for a summary of adverse events (AEs) and Section 6.3.4 for potential drug interactions associated with abiraterone.

1.1.1.2 Enzalutamide

Enzalutamide is an oral second generation AR inhibitor. It was approved by the FDA for the treatment of mCRPC in 2012. Enzalutamide is more potent and binds more tightly to the AR than the first generation androgen inhibitors. It also inhibits the translocation of the receptor to the nucleus and prevents association of the AR with nuclear deoxyribonucleic acid (DNA), actions not shared by the first generation blockers [37].

Similar to abiraterone, enzalutamide was first evaluated in a randomized phase 3 trial in mCRPC post docetaxel. Enzalutamide demonstrated significant improvements in PFS and OS as compared to placebo (8.3 vs 2.9 months; $p<0.001$ and 18.4 vs 13.6 months; $p<0.001$, respectively) in this trial [19]. The rate of CTC conversion from unfavorable to favorable status after 13 weeks of treatment across the 2 arms was 24% in the 217 patients evaluable for this endpoint. In addition, 36% of the 217 patients had a decline in CTCs from baseline of at least 30% after 13 weeks of treatment across the 2 arms [33]. In the subsequent phase 3 trial in the chemotherapy naïve mCRPC population, at the planned interim analysis (median 22 months of follow-up), enzalutamide significantly improved OS compared to placebo (32.4 vs 30.2 months; $p<0.001$). PFS at 12 months was also significantly improved with enzalutamide over placebo (65% vs 14%, $p<0.001$; median PFS for enzalutamide had not been reached at the time of this analysis). [20]. With longer follow-up (median duration 31 months), the PFS and OS benefits for enzalutamide were maintained, with a median OS of 35.3 vs 31.3 months, and a median PFS of 20 vs 5.4 months. Of note, this latter follow-up included 5 months of an open-label extension whereby placebo patients could cross over to enzalutamide [38].

See Section 9.3.3 for a summary of AEs and Section 6.3.3 for potential drug interactions associated with enzalutamide.

1.1.1.3 Mechanisms of Resistance to Second Generation Androgen Inhibition

Enzalutamide and abiraterone represent exciting new developments in the treatment of mCRPC, and are now established as standard of care treatments in this setting. Their success demonstrates that mCRPC remains driven by the AR, even after progression on ADT [8]. Unfortunately, 15-25% of patients are resistant when first treated with these agents [24], and of those who do respond, a large majority eventually develop resistance whether treated previously with chemotherapy or not. Progression in the chemotherapy naïve population develops within 1.5 to 2 years [38, 39]. When used post chemotherapy, progression develops sooner, generally within 6 to 8 months [17, 19].

In a post hoc analysis of the patients treated in the phase 3 abiraterone chemotherapy naïve trial, abiraterone retreatment (frequently after intervening chemotherapy) resulted in a PFS of only 3.9 months and a PSA50 of 43% (unconfirmed). One patient (2%) experienced radiologic improvement [40]. Subsequent use of the alternate agent (e.g., abiraterone after enzalutamide failure) has also been evaluated. Unfortunately, minimal activity has been seen when abiraterone is used after enzalutamide failure [41-43]. In the largest trial of repeat second generation androgen inhibition after progression on a second generation androgen inhibitor, 251 chemotherapy naïve patients were randomized after experiencing PSA progression on enzalutamide. Patients were randomized to either enzalutamide + abiraterone/prednisone or

placebo + abiraterone/prednisone until radiographic PFS, unequivocal clinical progression or death. In the placebo arm, PSA 50% response rate (PSA50) was 2.5% and median time to PSA progression was 2.8 months. Radiologic response to treatment was not reported [41]. In one small trial of abiraterone after patients had received docetaxel and enzalutamide, PSA50 was 8% (confirmed) and median PFS (with progression defined as either time to PSA, radiographic or clinical progression) was 2.7 months. In the 12 patients evaluable radiologically, 1 (8%) experienced a partial response (PR) [42]. In a second small study of abiraterone after patients had received docetaxel and enzalutamide, PSA50 was 3% (unconfirmed) and median time to progression (defined as either time to PSA, radiographic or clinical progression) was 3.8 months. No radiographic responses were observed [43].

When enzalutamide was used post abiraterone in the phase 3 population (with most patients receiving chemotherapy in the interim), PSA50 was 67% (unconfirmed) and median time to PSA progression was 2.8 months. One patient (3%) experienced radiologic improvement [40]. In several small retrospective series of enzalutamide post abiraterone and chemotherapy, PSA decreases of ≥50% were observed, but responses tended to be of short duration [44, 45]. The PSA50 in these series was 12.8% (confirmed) [45] or 28.6% (unconfirmed)[44], and the median time to PSA progression was either 2.7 [45] or 4 months [44]. Few patients in these series experienced a PR (1 of 17 [6%] evaluable patients [44] and 1 of 23 [4%] evaluable patients [45]). Another retrospective study evaluated enzalutamide post abiraterone in the chemotherapy-naïve population vs the chemotherapy pre-treated population, and concluded enzalutamide had limited activity regardless of prior docetaxel use (PSA50 of 26% vs 22% [confirmed], p=0.8 and median time to progression of 6.6 vs 4.6 months, p=0.6, for patients with no prior docetaxel vs prior docetaxel, respectively). Radiologic response to treatment was not assessed [46]. In a recent prospective study of enzalutamide in 214 patients with progressing mCRPC after ≥ 6 months of abiraterone (~30% received prior chemotherapy), the PSA50 was 27% (unconfirmed). Median radiographic PFS was 8.1 months and the median time to PSA progression was 5.7 months. Radiologic response to treatment was not reported [47]. In an observational study of 61 patients treated under an enzalutamide expanded access study who had previously been treated with docetaxel and abiraterone, PSA50 was 21%. Radiologic response to treatment was not reported [48]. In a similar population of 24 patients who received enzalutamide on a compassionate use basis post abiraterone and docetaxel, PSA50 was 17%, and radiologic response to treatment was not reported [49].

In a study of the investigational second generation androgen inhibitor apalutamide in chemotherapy-naïve patients with mCRPC who progressed after at least 6 months of abiraterone, the PSA50 (unconfirmed) was 22% (4 of 18 patients). Zero of 10 evaluable patients experienced a radiologic response [50].

Overall and based on the data just reviewed, it has been estimated that 13-29% of patients who receive enzalutamide post abiraterone will achieve a PSA 50% response. Patients who receive abiraterone post enzalutamide have a lower likelihood of achieving a PSA 50% response (≤ 8%) [51]. In both scenarios, objective responses are rare. These data highlight the problem of cross-resistance. Further, any benefit that is seen typically lasts for approximately half the duration compared to first-line therapy [24].

Research into the mechanisms of resistance to the second generation androgen inhibitors is

ongoing, and not yet clearly established. A number of potential mechanisms have been proposed and include (but are not limited to) amplification of the AR gene [29, 52], acquisition of AR mutations leading to non-specific activation of AR by weaker agonists, increased expression of CYP17 or the glucocorticoid receptor, and neuroendocrine trans-differentiation bypassing androgen dependence [53]. More than 100 somatic mutations in AR have been identified [53], and while rare in early stage disease, are relatively common (10-30%) in CRPC [28]. An additional mechanism seen as increasingly important in CRPC [54], and that has been implicated in both abiraterone and enzalutamide resistance, is development of abnormal splicing variants (V) of the AR messenger ribonucleic acid (mRNA). These splice variants, the most abundant of which is the variant termed AR-V7, result in a constitutively active AR [29, 55]. These variants lack the ligand binding domain, which is the therapeutic target of hormonal therapies, yet maintain the ability to homodimerize, translocate to the nucleus, and bind to and regulate DNA driving a gene expression program that promotes cancer growth [37].

The role of CTCs at baseline and during treatment is an exciting, increasingly active area of clinical research [56]. In a recent prospective study of 202 patients with mCRPC starting abiraterone or enzalutamide, investigators evaluated the ability of CTCs (CTCs +/-) and the presence of AR-V7 within the CTCs (+/-) to predict benefit from treatment [57]. CTC- patients experienced significantly better outcomes (PSA response*, PSA-PFS, PFS and OS) than CTC+ patients. Overall, 17.8% of patients with CTCs had AR-V7+ disease. In CTC+ patients, AR-V7+ was associated with poorer outcomes as compared to those that were CTC+/AR-V7- (PSA response of 13.9% vs 52.2%, PSA-PFS of 2.1 vs 6.2 months, PFS of 3.1 vs 7.7 months and OS of 11.2 vs 29.5 months). Because of the large sample size, investigators were able to separately analyze patients who were starting abiraterone or enzalutamide as second line (i.e., after having already received the alternate agent). A higher percentage of second line patients had AR-V7+ disease (26.9%) versus first line (12.1%), and outcomes were poorer compared to first line (PSA response of 4.8% vs 26.7%, PSA-PFS of 1.1 vs 2.9 months, PFS of 2.8 vs 3.1 months and OS of 8.5 vs 21.5 months). *PSA response was defined as the proportion of patients with a ≥50% PSA decline from baseline (PSA50) at any time point after therapy (and maintained for ≥ 3 weeks).

Another mechanism of resistance to anti-androgen therapy relates to the capacity of adenocarcinoma of the prostate to acquire neuroendocrine characteristics (referred to as lineage plasticity). Researchers have estimated that this evolution from adeno- to endocrine may occur in ~25% of CRPC tumors [58], and may be related to alterations in the retinoblastoma 1 (RB1) and TP53 genes [58-60]. The frequency of alterations in both of these genes is significantly higher in tumors from patients who progressed while undergoing treatment with either of the second generation androgen inhibitors as compared to patients who had not received treatment with a second generation androgen inhibitor [59]. In a mouse model of adenocarcinoma of the prostate, deletion of the RB1 gene (referred to as double knock out or DKO as this model is also PTEN-) led to a more aggressive tumor that progressed from adenocarcinoma to one with markers of both adenocarcinoma and neuroendocrine disease. Most of these tumors responded (at least transiently) to castration. In the mouse model where both RB1 and Tp53 were deleted (referred to as triple knock out or TKO), tumors were even more aggressive and castrate resistant de novo, with reduced dependence on AR signaling [60]. Gene expression of the DKO and TKO models showed an increased expression of neuroendocrine lineage genes and the AR coactivator EZH2 (Enhancer of Zeste Homolog 2; see Section 1.2), along with other changes. In cell lines produced

from the DKO and TKO mouse models, inhibitors against EZH2 increased AR expression and restored sensitivity to enzalutamide; these findings were reproduced with analogous cell lines developed from human tumors. In a post castration recurrent DKO mouse model, treatment with an EZH2 inhibitor plus enzalutamide significantly slowed tumor growth as compared to enzalutamide alone [60]. These data suggest EZH2 inhibitors in combination with anti-androgens represent a novel strategy worthy of study in mCRPC, particularly in those with features of neuroendocrine disease [58]. As such, we plan to focus on this specific population in a separate study.

1.2 EZH2 in Prostate Cancer

EZH2 is the catalytic component of a large, multi-protein complex called Polycomb Repressive Complex 2 (PRC2), which generally functions in transcriptional repression. PRC2's role in gene silencing is largely dependent on the catalytic activity of EZH2 or its paralog EZH1. These are the only enzymes known to catalyze trimethylation of lysine 27 of histone 3 (H3K27me3). The mechanism of EZH2-mediated gene silencing includes: (1) Placement of H3K27me3 at gene promoters serves as a recognition site for other chromatin regulators that promote chromatin compaction and thereby prevent binding of transcription factors and the transcription machinery; (2) Placement of H3K27me3 at genes provides a transcriptional 'roadblock', thus impeding efficient transcription of the DNA template; and (3) The placement of H3K27me3 precludes placement of histone modifications that facilitate enhancer licensing, transcription initiation and elongation.

EZH2 is upregulated in metastatic prostate cancer (as compared to localized disease) [61], and higher levels are associated with more aggressive disease [62]. The expression of EZH2 is increased in prostate cancer models known to be castrate resistant, with reduced dependence on AR signaling. EZH2 is important for prostate cancer lineage plasticity in the context of TP53 and RB1 deficiency and EZH2 inhibitors restore AR expression and sensitivity to enzalutamide [60]. EZH2 has also been established as a key driver of metastasis in prostate cancer via activation of Ras and nuclear factor-kappa B (NF-kB) [63]. Silencing of EZH2 with small interfering ribonucleic acid (siRNA duplexes targeted against EZH2) has been shown to inhibit prostate cancer cell proliferation *in vitro* [61] and *in vivo* [64].

EZH2 inhibitors effectively suppressed the growth of AR-positive prostate cancer models *in vitro*, including ARV7-driven 22RV1 cells. In an engineered model of prostate cancer progression (inducible overexpression of AR in LNCaP cells), sensitivity to EZH2 inhibitors increased with increased AR levels. Moreover, EZH2 inhibitors synergized with enzalutamide to suppress the growth of LNCaP prostate cancer cells, suggesting a functional cooperation of EZH2-mediated chromatin regulation and AR signaling pathways in prostate cancer cells. Consistent with this observation, EZH2 inhibition in rats and dogs resulted in dose dependent, reversible testicular degeneration, prostate atrophy and degeneration of the tubular seminiferous epithelium (Constellation Pharmaceuticals, Inc. [CPI], unpublished data).

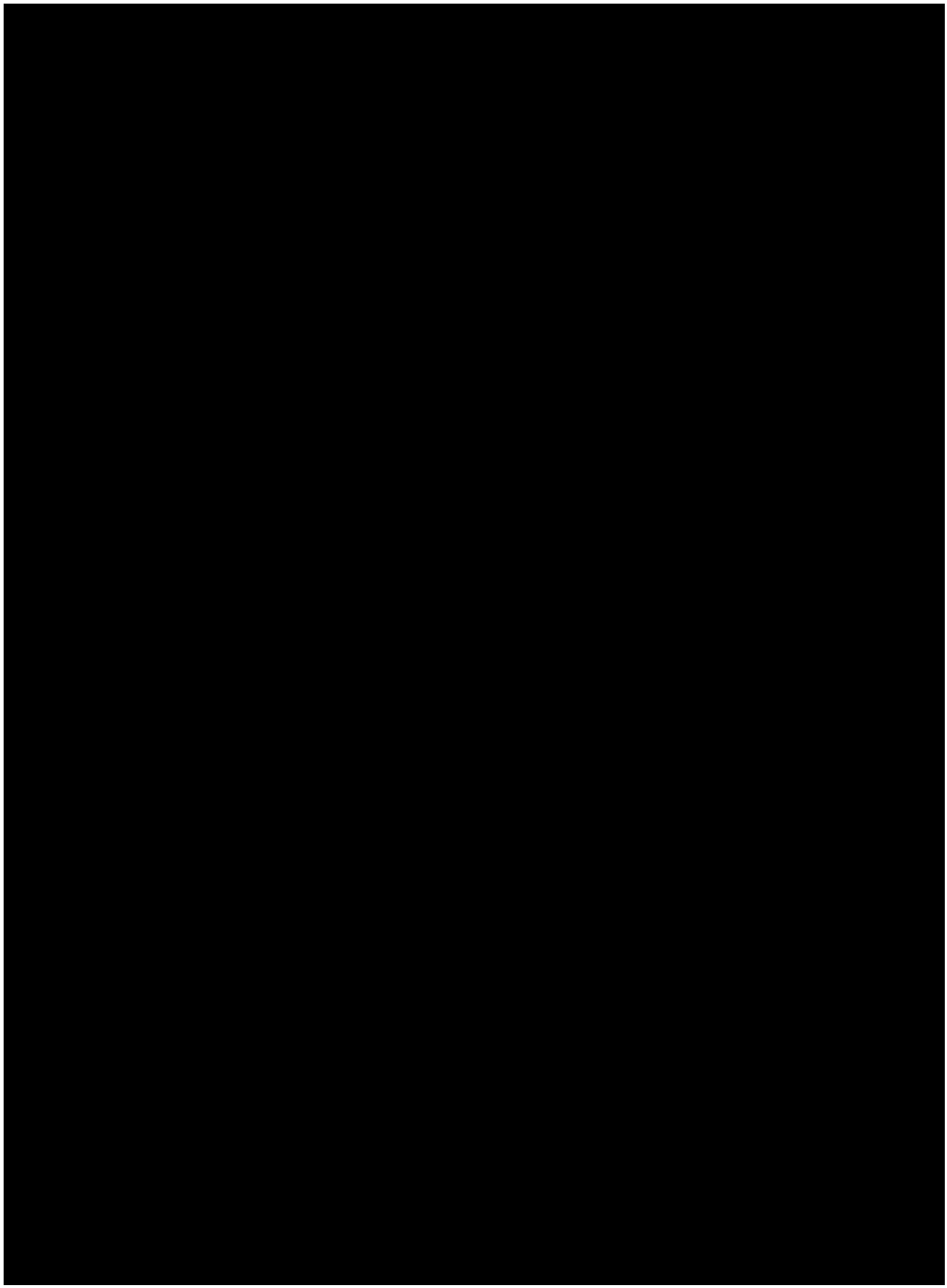
1.3 CPI-1205

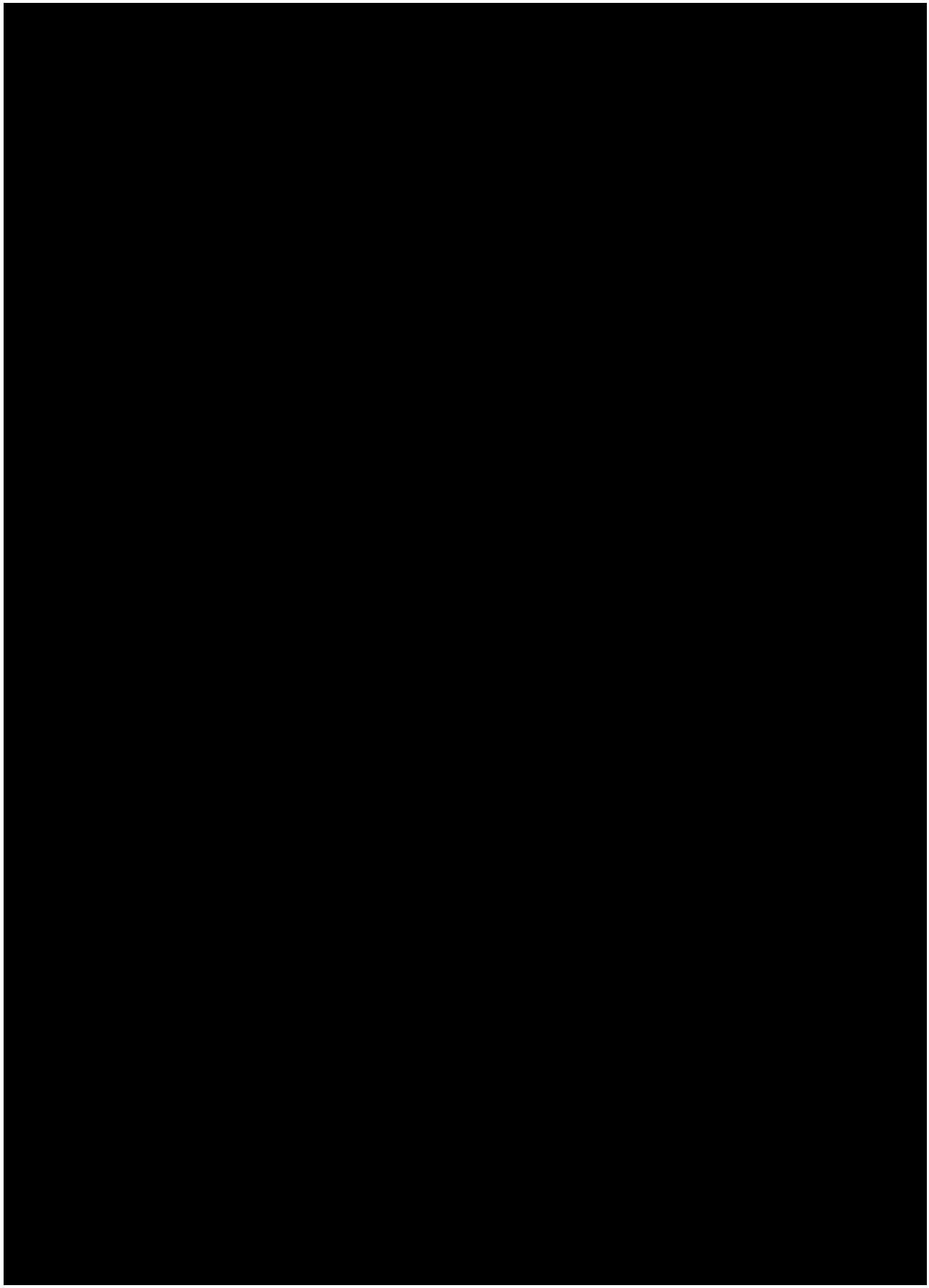
1.3.1 Description

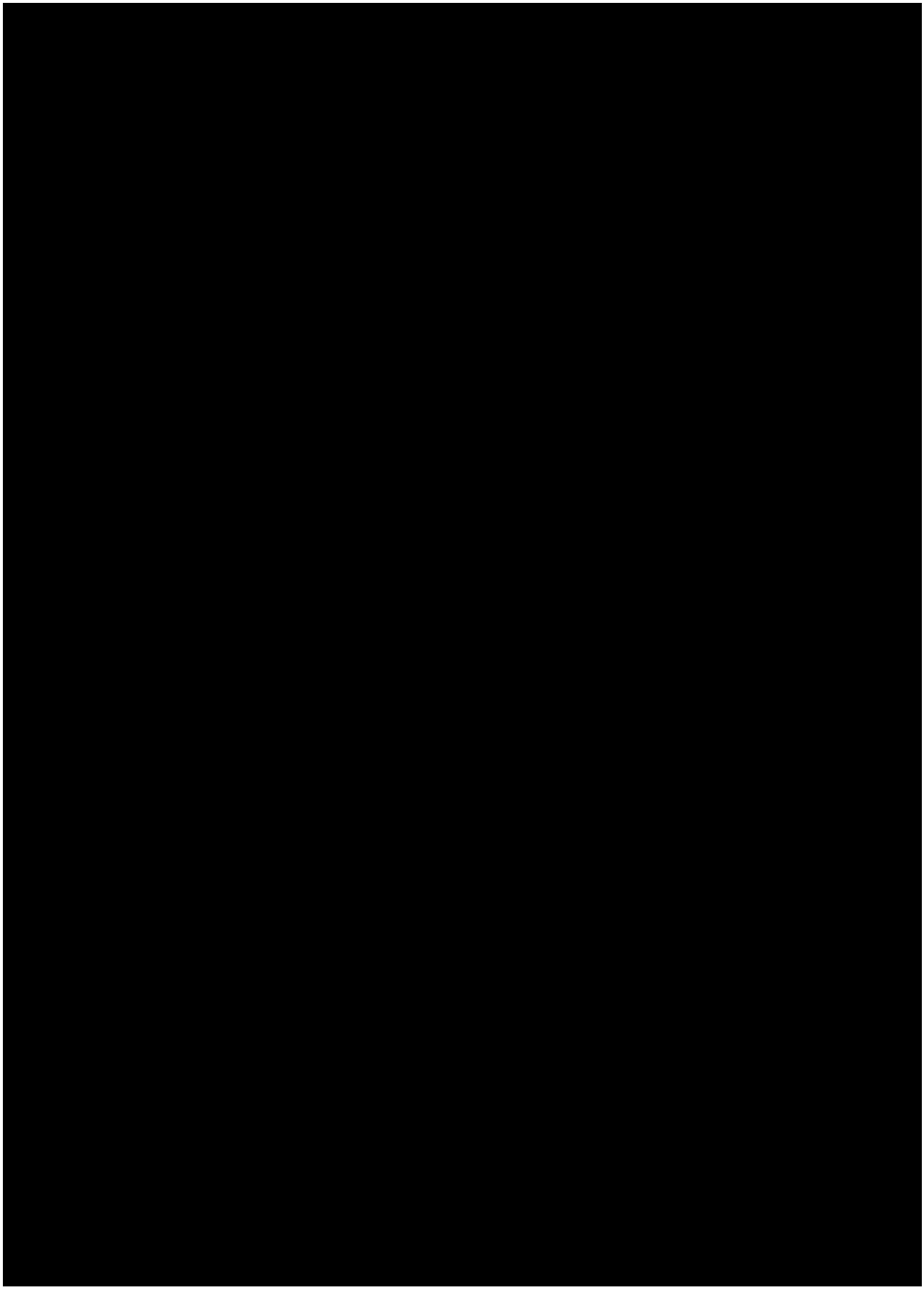
CPI-1205 is a small molecule inhibitor of the catalytic activity of EZH2. CPI-1205 has a molecular weight of [redacted]

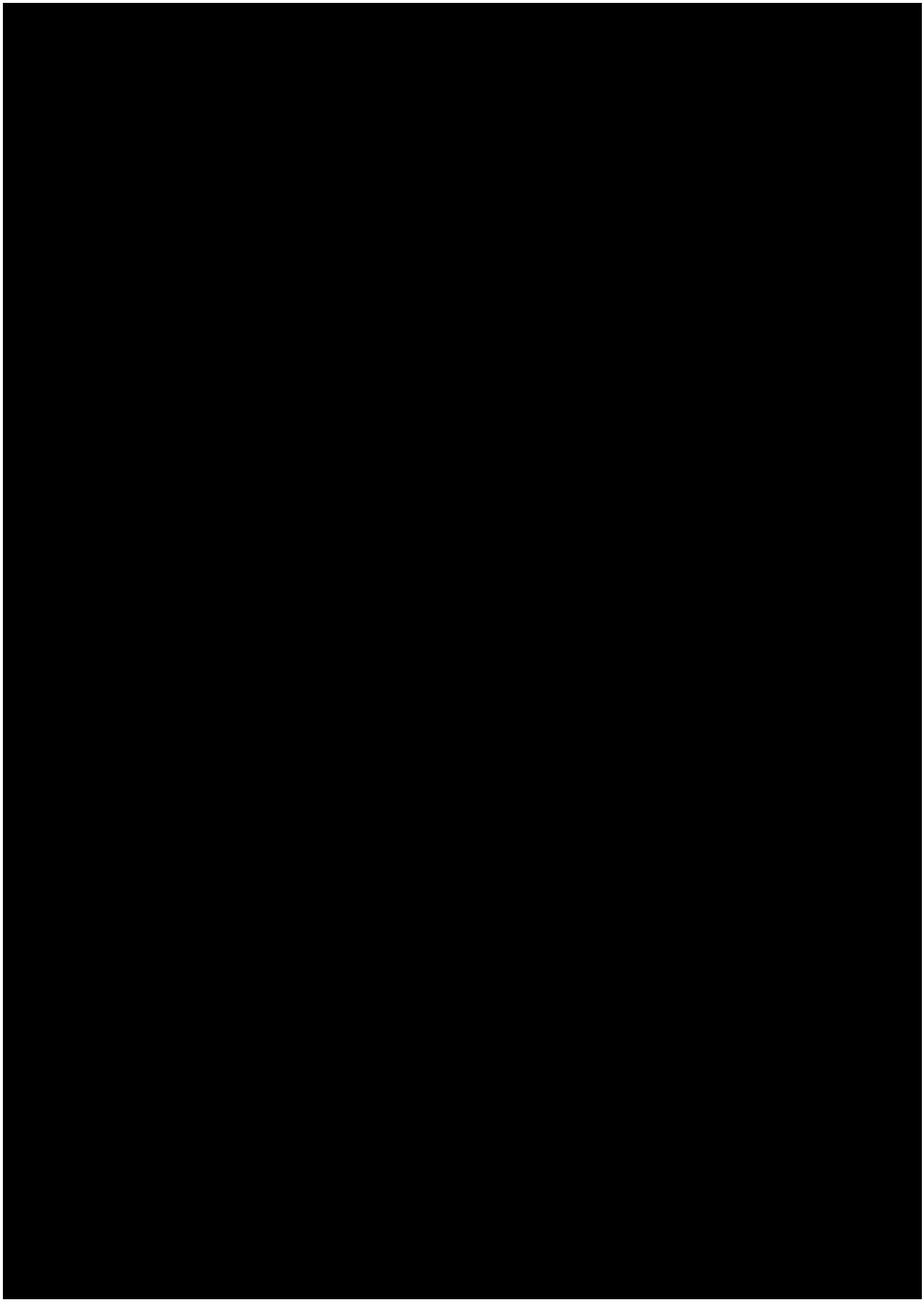
The following sections summarize the preclinical data for CPI-1205. Additional details are available in the Investigator's Brochure (IB).

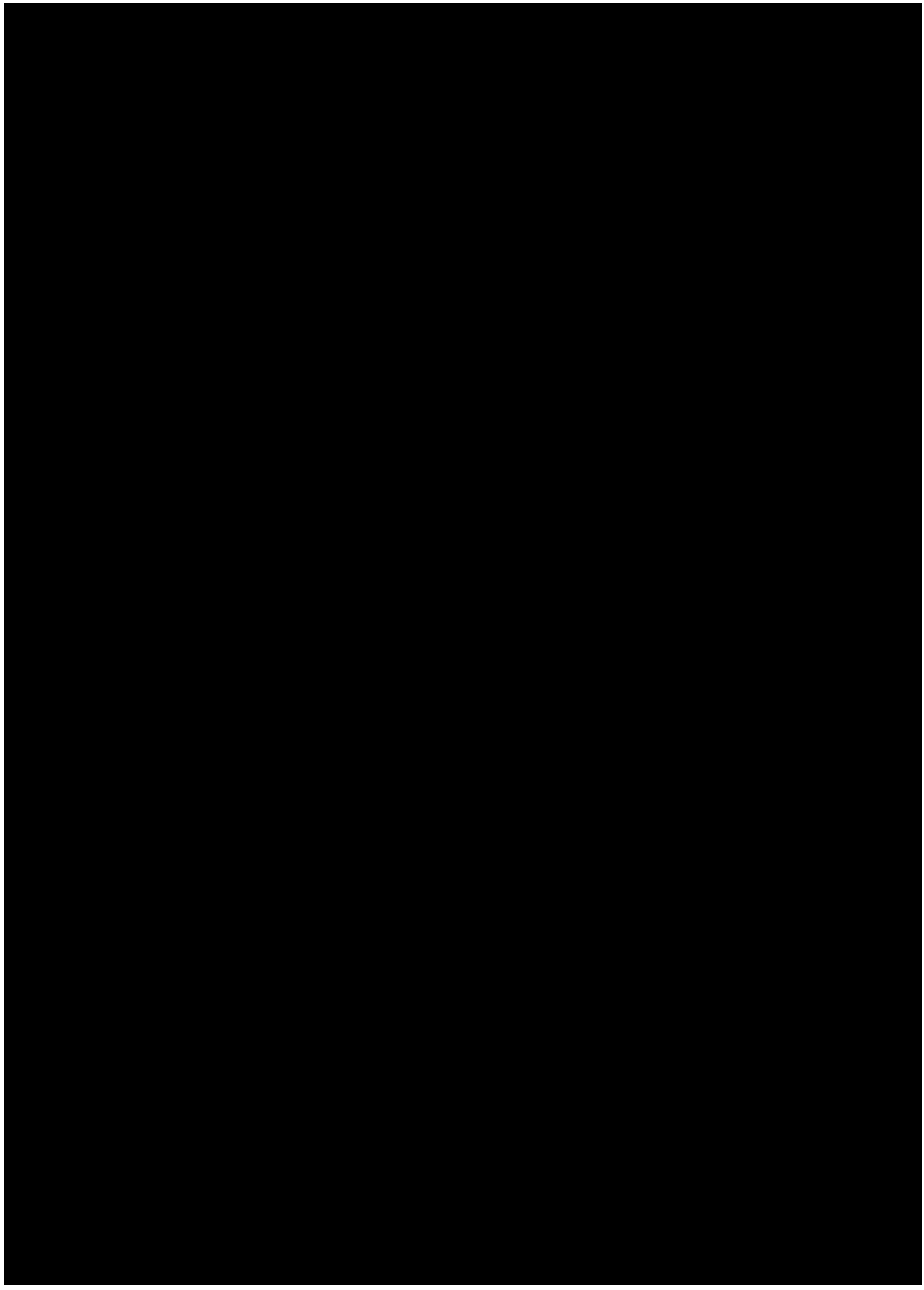
[redacted]

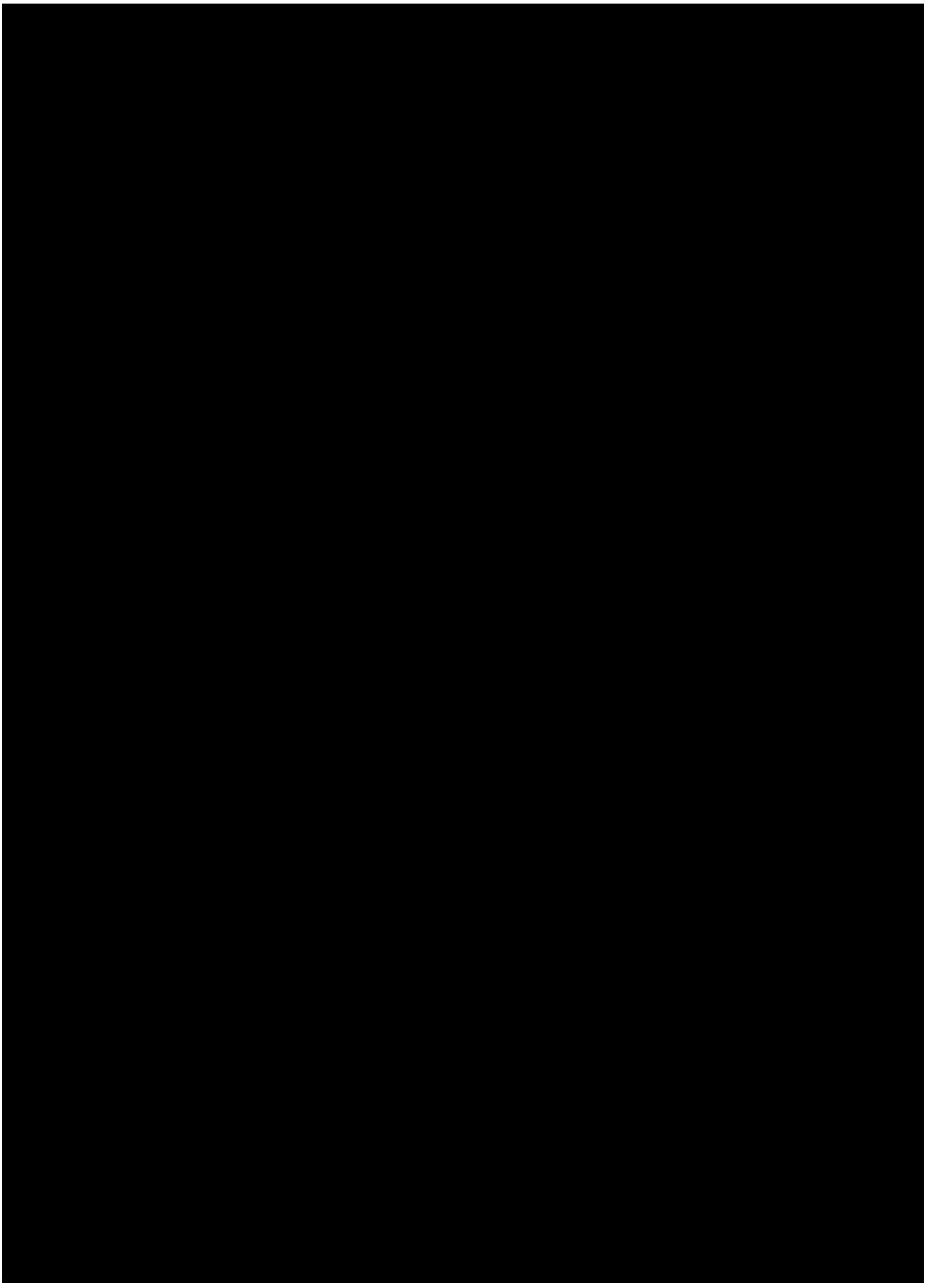


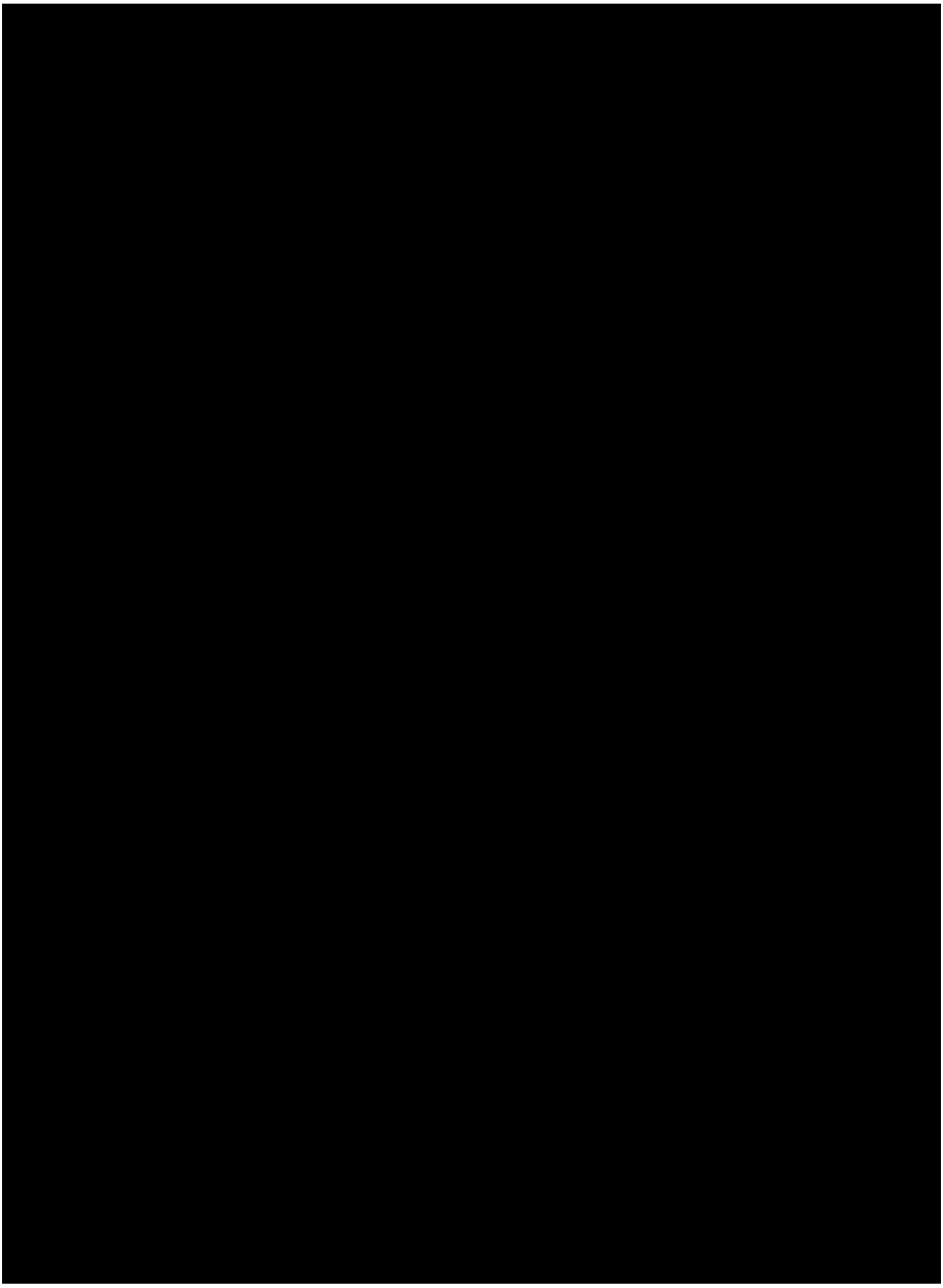












1.4 Study Rationale and Design

1.4.1 Study Rationale

1.4.1.1 Treatment of mCRPC

Notwithstanding the availability of 4 new treatments for mCRPC since 2010, the disease remains incurable, and long term outcomes are poor. Resistance to second generation androgen inhibitors, the class of new drugs with the broadest application in mCRPC, occurs in almost all patients. Unfortunately, cross-resistance between abiraterone and enzalutamide is common, and any responses with subsequent treatment with the alternative agent are of short duration [24].

The mechanisms behind resistance are complex, but increasing evidence establishes a role for EZH2 in two of the more prominent mechanisms of resistance proposed by researchers. First, EZH2 appears to be critical in the progression of androgen sensitive adenocarcinoma of the prostate to androgen resistant prostate cancer with neuroendocrine features. Second, there is evidence for a relationship between the splice variant, AR-V7, and EZH2. AR-V7 is associated with poor outcomes and is expressed at a higher frequency after progression on second generation androgen inhibitors [57].

[redacted]

Taken together, and particularly when combined with the preliminary efficacy data as summarized in Section 1.3.3.6, these data support the possibility that CPI-1205 when combined with abiraterone or enzalutamide may help overcome resistance in mCRPC patients previously treated with a second generation androgen inhibitor.

1.4.1.2 Cobicistat to Improve PK Profile of CPI-1205

In preclinical animal models and as outlined in Section 1.3.2.2, the antitumor effect associated with CPI-1205 appears to be positively correlated with increased AUC. Thus, efforts to increase AUC may lead to more profound and sustainable antitumor activity. [redacted]

Cobicistat (Tybost®) is a CYP3A inhibitor approved by the FDA to increase systemic exposure of the CYP3A substrates atazanavir or darunavir, antiretroviral agents used in the treatment of human immunodeficiency virus (HIV). This approval was based on a phase 3 trial comparing cobicistat (150mg PO daily) versus ritonavir as pharmacokinetic enhancers of atazanavir when combined with emtricitabine/tenofovir disoproxil fumarate (DF) in treatment-naive patients infected with HIV Type 1 (HIV-1). Safety across the two arms was very similar, indicating that cobicistat did not adversely impact the safety of the atazanavir combination arm [67]. Cobicistat is also a component of the FDA approved drugs Stribild® (comprised of cobicistat, elvitegravir, emtricitabine and tenofovir DF), Prezcobix® (comprised of cobicistat and darunavir) and Evotaz® (comprised of cobicistat and atazanavir), all indicated for the treatment of HIV-1. Cobicistat is included to increase the systemic exposure of HIV patients to elvitegravir, darunavir and atazanavir within the respective products. Of note, cobicistat causes increases in serum creatinine and decreases in estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function (www.tybost.com). This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating cobicistat, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance. Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL from baseline should be closely monitored for renal safety.

[redacted]

Cobicistat was well tolerated when administered at 300 mg QD for 7 days and 14 days in two separate healthy volunteer studies [68, 69]. In addition, cobicistat was found to be well tolerated when administered at 150 mg BID for 10 days to healthy volunteers [70] The higher dose regimens of cobicistat have not been pursued not because of any safety concerns, but because a

single daily dose of cobicistat at a dose of 150 mg is sufficient to inhibit CYP3A4 when used with antiretrovirals [68]. Cobicistat has also been safely dosed up to 4 times daily for a total of 15 months in a patient who had sub-therapeutic levels of axitinib for the treatment of renal cell carcinoma [71].

1.4.2 Study Design

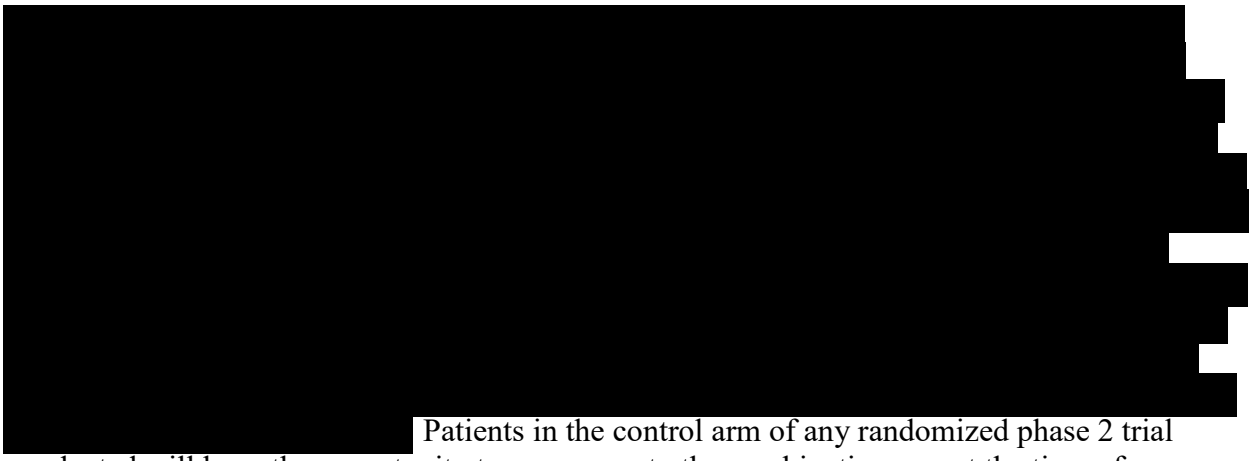
CPI-1205-201 is a phase 1b/2, multi-center, open-label study of CPI-1205 alone and with cobicistat in combination with either enzalutamide or abiraterone/prednisone in patients with mCRPC already treated with a second generation androgen inhibitor. During the phase 1b dose escalation part of the study, patients must have been treated with at least one second generation androgen inhibitor (prior chemotherapy is also allowed). Prior to Amendment 2, patients were enrolled into phase 1b Dose Level 1A (CPI-1205 PO TID + enzalutamide or abiraterone/prednisone). As of Amendment 2, new patients will be enrolled into cohorts of dose escalated CPI-1205 PO BID in combination with fixed dose cobicistat PO BID. Patients will be enrolled in either the CPI-1205/cobicistat + enzalutamide combination or the CPI-1205/cobicistat + abiraterone/prednisone combination. Cobicistat dosing will begin with one dose the evening prior to day 1 of CPI-1205 (i.e., the evening of day 0), and then continue PO BID starting on day 1 of CPI-1205. See Section 6.1 for rules regarding drug administration and food. Enrollment in these two combinations will occur simultaneously. Based on emerging data, the SSC may elect to enroll additional new patients into the TID cohorts (without cobicistat) or add BID cohorts (without cobicistat).

Following determination of the MTD in each of the CPI-1205 BID + cobicistat combinations (and possibly in the CPI-1205 TID combinations) and after evaluation of the BID cohorts without cobicistat (if applicable) during phase 1b dose escalation, only one of the CPI-1205 dosing schedules will be selected as the recommended Phase 2 dose (RP2D) for each combination (i.e., with either enzalutamide or abiraterone/prednisone).

As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population. To be included in a heavily pretreated expansion cohort (HPEC), patients must have had prior treatment with and progressed on chemotherapy in the mCRPC setting, and must have been treated with and progressed on two lines of a second generation androgen inhibitor (one from each class). Patients must also have at least one measurable lymph node. [redacted] **NOTE:** the SSC will recommend which regimen(s) and dose to evaluate in the HPEC(s) based on safety, PK, efficacy, etc. **NOTE:** a Simon's 2-stage design will be used for any HPEC that opens. After enrollment of [redacted] patients (stage 1), the SSC will recommend whether to continue to stage 2 at the current dose and schedule based on efficacy, or whether a change in CPI-1205 schedule (e.g., from TID without cobicistat to BID with cobicistat) is warranted based on safety, PK, efficacy, etc. The primary endpoint for the HPEC(s) is objective response rate (ORR) as determined by

CRR.

One or both of the CPI-1205 combinations evaluated during phase 1b dose escalation (i.e., CPI-1205 [with or without cobicistat] in combination with either enzalutamide or abiraterone/ prednisone) may proceed to phase 2 after consideration of PK and pharmacodynamic results, data from the HPEC(s), as well as safety data. **NOTE:** phase 2 may begin prior to the completion of the HPEC(s). During phase 2, enrollment will be limited to patients who have received only one second generation androgen inhibitor (from a different class than the agent chosen for the applicable phase 2), who progressed after at least 24 weeks of treatment with the second generation androgen inhibitor, and who have not received prior chemotherapy for mCRPC. In addition, at least 50% of patients enrolled in any phase 2 trial that is opened must have measurable soft tissue disease.



Patients in the control arm of any randomized phase 2 trial conducted will have the opportunity to cross over to the combination arm at the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE once the decision is made to initiate another systemic treatment for prostate cancer, and provided they are eligible (see Section 5.5.1).

Safety will be closely monitored in this trial, will guide dose escalation during phase 1b and will determine whether phase 1b HPEC(s) should be opened. Potential overlapping toxicities of CPI-1205 when combined with either enzalutamide or abiraterone include [redacted] Patients will be carefully monitored for these as well as other AEs, with doses modified when necessary as outlined in Section 6.2. Efficacy will be assessed via enumeration of CTCs, PSA, imaging (including computed tomography (CT)/magnetic resonance imaging (MRI) and bone scans), and pain/analgesic usage. Patients will also be followed for skeletal-related events (SREs), symptomatic skeletal events (SSEs) and unequivocal clinical progression, and quality of life and patient reported outcomes will be evaluated.

CTCs will be enumerated using the assay approved by FDA for *in vitro* diagnostic use, as presence of CTCs (≥5 CTCs per 7.5 mL blood) has been found to be associated with significantly worse OS [72]. In addition, both conversion from unfavorable to favorable CTC status and a decline of at least 30% in CTCs from baseline in patients with an unfavorable CTC status are associated with increased OS [33, 34]. While both CTC conversion and CTC 30% response are likely informative, CTC 30% response may be particularly useful because as noted by Lorente et al, "it is difficult to consider a patient whose CTC count falls from 100 to 5 cells/

7.5ml after three cycles as a 'nonresponder' while considering a patient whose CTC count falls from 5 to 4 cells/7.5ml as a 'responder'" [34]. Limited data are available on the conversion rate of CTCs from an unfavorable to favorable status after treatment with second generation androgen inhibitors in patients previously treated with a second generation androgen inhibitor. This endpoint was evaluated in a phase 1/2 trial of the investigational agent darolutamide in patients previously treated with a different second generation androgen inhibitor. None of the 13 patients who had an unfavorable status at baseline and a repeat CTC measurement after 12 weeks of treatment converted [73]. No data are available for CTC 30% response in this population.

In this study, treatment will continue until radiographic disease progression (as determined by the investigator), unequivocal clinical progression or a SRE (see Section 10 for definitions) **AND** planned initiation of another systemic treatment for prostate cancer. Of note, as outlined in Section 1.2, inhibitors of EZH2 restore AR expression, and could lead to an initial increase in PSA. Therefore, PSA rise without evidence of radiographic progression, unequivocal clinical progression or without a SRE will not be a criterion to discontinue study treatment.

NOTE: At the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE, patients enrolled in Dose Level 1A who receive CPI-1205 PO TID without cobicistat may have the option to switch to CPI-1205 PO BID with cobicistat at the discretion of the investigator, and only after consultation with the Medical Monitor. See Section 5.4.9.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Phase 1b Dose Escalation: Primary Objective

To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of CPI-1205 + enzalutamide and CPI-1205 + abiraterone/prednisone in patients with metastatic castration resistant prostate cancer (mCRPC). **NOTE:** The MTD will be determined for CPI-1205 PO BID with cobicistat for each combination. The SSC may also elect to determine the MTD for CPI-1205 PO TID, however, only one of the CPI-1205 dosing schedules (i.e., either TID or BID with cobicistat) will be selected as the RP2D for each combination.

2.1.2 Phase 1b Dose Escalation: Secondary Objectives

- To characterize the safety and tolerability profile of CPI-1205 (with or without cobicistat) + enzalutamide and CPI-1205 (with or without cobicistat) + abiraterone/prednisone.
- To characterize the pharmacokinetic (PK) profiles of CPI-1205, cobicistat, enzalutamide and abiraterone, and evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.
- To evaluate preliminary signs of efficacy of CPI-1205 (with or without cobicistat) + enzalutamide and CPI-1205 (with or without cobicistat) + abiraterone/prednisone.
- [redacted]

As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population (referred to as HPEC[s]). See Section 5.4.7 for additional details on the population to be enrolled and choice of regimen(s) for the HPEC(s).

2.1.3 Phase 1b HPEC(s): Primary Objective

To estimate objective response rate (ORR) as determined by central radiology review (CRR) of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone in the HPEC.

2.1.4 Phase 1b HPEC(s): Secondary Objectives

NOTE: radiographic response and progression are defined per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria.

- To characterize the safety and tolerability profile of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone in the heavily pretreated population.

- To estimate ORR as determined at the site by the investigator.
- To estimate ORR (excluding parenchymal lesions) as determined by CRR.
- To estimate prostate specific antigen (PSA) 50% response rate (PSA50).
- To estimate time to PSA progression.
- To estimate radiographic progression free survival (rPFS) as determined by CRR and at the site by the investigator.
- To estimate overall survival (OS).
- To estimate duration of response (DOR) as determined by CRR and at the site by the investigator and DOR (excluding parenchymal lesions) as determined by CRR.
- To estimate the time to first skeletal-related event (SRE) and the time to first symptomatic skeletal event (SSE).
- To estimate time to unequivocal clinical progression.
- To estimate time to initiation of new systemic treatment for prostate cancer.
- [redacted]
- To estimate the time to pain progression and the time to opioid analgesics.
- To estimate the circulating tumor cells (CTC) 30% response rate and CTC conversion rate in patients with unfavorable CTCs.
- [redacted]
- To further characterize the PK profiles of CPI-1205, cobicistat (if applicable), enzalutamide or abiraterone, and further evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.

Following determination of the MTD and RP2D during phase 1b dose escalation, one or both of the second generation androgen inhibitor combinations (i.e., CPI-1205 [with or without cobicistat] in combination with either enzalutamide or abiraterone/prednisone) may proceed to phase 2 after consideration of PK, pharmacodynamic results, data from the HPEC(s) and safety data. [redacted]

[redacted]

2.1.5 Randomized Phase 2: Primary Objective

To evaluate the effect of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone (combination arm) versus(vs) enzalutamide **OR** abiraterone/prednisone alone (control arm) in patients with mCRPC.

2.1.6 Randomized Phase 2: Secondary Objectives

NOTE: radiographic response and progression are defined per the PCWG3 criteria and may be evaluated by CRR and at the site by the investigator. ORR (excluding parenchymal lesions) and DOR (excluding parenchymal lesions) will only be evaluated by CRR.

NOTE: The combination arm referred to in the objectives below may be with or without cobicistat.

- To compare rPFS and rPFS at 3 months between the combination arm and control arm.
- To compare time to PSA progression between the combination arm and control arm.
- To compare ORR and DOR in patients with soft tissue disease between the combination arm and control arm.
- To compare ORR (excluding parenchymal lesions) and DOR (excluding parenchymal lesions) in patients with non-parenchymal soft tissue disease between the combination arm and the control arm.
- To compare the composite response rate (where response is defined as PSA 50% response or objective response) in patients with soft tissue disease between the combination arm and the control arm.
- To compare the composite response rate (where response is defined as PSA 50% response or CTC 30% response) in patients with unfavorable CTCs between the combination arm and the control arm.
- To compare the time to first SRE and the time to first SSE between the combination arm and control arm.
- To compare the time to unequivocal clinical progression between the combination arm and control arm.
- To compare the time to initiation of new systemic treatment for prostate cancer between the combination arm and control arm.

- To compare the time to pain progression and the time to opioid analgesics between the combination arm and control arm.
- To compare the CTC 30% response rate and CTC conversion rate in patients with unfavorable CTCs between the combination arm and control arm.
- To compare OS between the combination arm and the control arm.

- To evaluate the safety of CPI-1205 in combination with enzalutamide **OR** abiraterone/prednisone (combination arm).
- In the combination arm(s) only to further characterize the PK profiles of CPI-1205, cobicistat (if applicable), enzalutamide or abiraterone, and further evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.

2.1.7 Single Arm Phase 2: Primary Objective

- To evaluate the effect of the combination selected for the single arm phase 2.

2.1.8 Single Arm Phase 2: Secondary Objectives

- **NOTE:** If a single arm phase 2 is conducted, the same endpoints will be evaluated as for the randomized phase 2, but they will be estimated or evaluated for the single arm rather than compared as for the randomized phase 2.

.

[redacted]

2.2 Endpoints

2.2.1 Phase 1b Dose Escalation: Primary Endpoint

The MTD will be determined based on the rate of dose-limiting toxicities (DLTs). The RP2D will be selected based on PK and the overall tolerability of the combination, but will not exceed the MTD. See Sections 5.4.4, 5.4.5 and 5.4.6 for additional information.

2.2.2 Phase 1b HPEC(s): Primary Endpoint

ORR is defined as the proportion of patients with a complete response (CR) or partial response (PR) per PCWG3 and as determined by CRR (see Section 10.2.3). **NOTE:** all patients in the HPEC(s) must have at least one measurable lymph node at study entry.

2.2.3 Randomized and Single Arm Phase 2: Primary Endpoints

The co-primary endpoints include the following:

- PSA50 is defined as the proportion of patients who have a ≥50% reduction in PSA from baseline (see Section 10.1.2), after at least 1 dose of study treatment.

- The composite response rate is defined as the proportion of patients who have either a CTC 30% response or an objective response after at least 1 dose of study treatment.

    - CTC 30% response is defined as a ≥30% reduction in CTCs from baseline in patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood; see Section 10.5).

    - Objective response is defined as a CR or PR per PCWG3 in patients who enter the trial with measurable soft tissue disease (see Section 10.2.3). Response will be based on CRR.

NOTE: At least 50% patients in phase 2 must have measurable soft tissue disease at study entry.

2.2.4 Secondary Efficacy Endpoints

NOTE: Details about the PCWG3 criteria [56] and efficacy endpoints can be found in Section 10.

NOTE: For phase 1b dose escalation, any of the endpoints defined below may be used to evaluate preliminary signs of efficacy unless otherwise noted.

- PSA50 is defined as the proportion of patients with a ≥50% reduction in PSA from baseline. **NOTE:** this is only a secondary endpoint for phase 1b.

- Time to PSA progression is defined as the time from day (D) 1 of treatment to the date of PSA progression. See Section 10.1.3 for definitions of PSA progression.

- rPFS is defined per PCWG3 as time from D1 of treatment to the date when the first site of disease is found to progress (using a manifestation-specific definition of progression), or death, whichever occurs first. The proportion of patients who remain radiographic progression free at 3 months will also be assessed.

- For patients with measurable soft tissue disease, ORR is defined as the proportion of patients with a CR or PR per PCWG3. DOR is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3.

- In patients with measurable disease in non-parenchymal soft tissue, ORR (excluding parenchymal lesions) is defined as the proportion of patients with a CR or PR per PCWG3 in soft tissue excluding the parenchyma (i.e., liver and lung). DOR (excluding parenchymal lesions) is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3 in soft tissue excluding the parenchyma.

- For patients with measurable soft tissue disease, an additional composite response rate is defined as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or an objective response (CR or PR per PCWG3). **NOTE**: this endpoint applies only to phase 2.

- In patients with unfavorable CTCs, an additional composite response rate is defined as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or a CTC 30% response (≥30% reduction in CTCs from baseline). **NOTE**: this endpoint applies only to phase 2.

- OS is defined as the time from D1 of treatment to the date of death. **NOTE**: this endpoint applies only to the phase 1b HPEC(s) and phase 2.

- Time to first SRE is defined as the time from D1 of treatment to the date of first SRE. Time to first SSE is defined as the time from D1 of treatment to the date of first SSE. See Section 10.6 for definitions of SRE and SSE.

- Time to unequivocal clinical progression is defined as the time from D1 of treatment to the date of unequivocal clinical progression. See Section 10.4 for definition of unequivocal clinical progression.

- Time to initiation of new systemic treatment for prostate cancer is defined as the time from D1 of treatment to the date any new systemic treatment for prostate cancer is initiated.

[redacted]

- Time to pain progression is defined as the time from D1 of treatment to the date of pain progression (pain progression defined in Section 10.7). For patients who enter the trial not on opioid analgesics, time to opioid analgesics is defined as the time from D1 of treatment to the date of first opioid usage.

- In patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood), conversion to favorable status is defined as four or fewer cells per 7.5 mL of blood. The CTC conversion rate is the proportion of patients who convert to favorable status.

- In patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood), the CTC 30% response rate is defined as the proportion of patients who have a ≥30% reduction in CTCs from baseline.

2.2.5 NOTE: **For phase 1b and any single arm phase 2 that opens, endpoints will be estimated. For any randomized phase 2 that is opened, the treatment difference will be evaluated.Additional Secondary Endpoints**

- AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). Laboratory evaluations, vital signs, physical examinations, and ECGs will also be evaluated.

- PK parameters will include: area under the concentration versus time curves $(AUC)_{last}$, maximum concentration (C_{max}), time to maximum concentration (T_{max}), minimum (trough) concentration (C_{trough}; defined as the level at 24 hours post dose or the level pre dose), peak-to-trough ratio and accumulation ratio (for both C_{max} and AUC_{last}).

[redacted]

3 STUDY POPULATION

The patients enrolled in this study will be adults (aged ≥ 18 years) with a histologically confirmed diagnosis of metastatic adenocarcinoma of the prostate that has progressed in the setting of medical or surgical castration (i.e., mCRPC). During phase 1b dose escalation, prior treatment for mCRPC must have included at least one line with a second generation androgen inhibitor (prior chemotherapy is also allowed). For the phase 1b HPEC(s), prior treatment must have included and patient must have progressed on chemotherapy in the mCRPC setting, and patients must have been treated with and progressed on two lines of therapy with a second generation androgen inhibitor, one from each class (i.e., a CYP17 inhibitor [e.g., abiraterone, orteronel] **AND** an AR inhibitor [e.g., enzalutamide, apalutamide]). The last second generation androgen inhibitor treatment received must not be from the same class as that incorporated in the applicable HPEC; i.e., if the HPEC incorporates enzalutamide, the last second generation androgen inhibitor therapy cannot be enzalutamide, apalutamide, etc. Patients must also have at least one measurable lymph node. During phase 2, enrollment will be limited to patients who have received only one line of a second generation androgen inhibitor (from a different class than the agent chosen for the applicable phase 2 study), who progressed after at least 24 weeks of treatment with the second generation androgen inhibitor, and who have not received prior chemotherapy for mCRPC. During phase 1b and 2, progressive disease may present as PSA, soft tissue and/or bone disease progression. During phase 2, at least 50% patients must also have measurable soft tissue disease.

The Screening period includes the 28 days before day 1 of treatment. During this time the eligibility of a patient for the study should be established by evaluating all relevant inclusion and exclusion criteria. A record documenting confirmation of the patient's eligibility must be stored with the source documentation at the study site.

3.1 Recruitment

Recruitment and enrollment strategies for this study may include recruitment from the investigators' local practices or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Any other arrangements will be described in the study manual.

3.2 Inclusion Criteria for Phase 1b Dose Escalation

Patients must meet all of the following criteria to be enrolled in this study:

1. Age ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix 1)
3. Life expectancy of at least 12 weeks
4. Histologically or cytologically confirmed adenocarcinoma of the prostate; **NOTE**: pure small cell carcinoma is excluded.
5. Documented metastatic disease.

6. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue gonadotropin-releasing hormone (GnRH) analog or antagonist (medical castration)
7. Serum testosterone <50 ng/dL
8. Progressive disease in the setting of medical or surgical castration (i.e., CRPC) as assessed by the investigator and that includes at least one of the following:
    a. Evidence of progression as measured by PSA increase of ≥25% and an absolute increase of ≥2 ng/mL in < 6 months from end of last therapy prior to enrollment; **NOTE**: increase should be measured from nadir (in patients with a decline in PSA during last therapy) or baseline (in patients without a decline in PSA during last therapy **AND/OR**
    b. Soft tissue disease progression as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [74] **AND/OR**
    c. Bone disease progression defined by two or more new lesions on bone scan
9. Bisphosphonate or denosumab therapy allowed provided dose has been stable for ≥ 4 weeks prior to day 1 of treatment
10. Prior treatment:
    a. Prior treatment for mCRPC must have included at least one line with a second generation androgen inhibitor (e.g., abiraterone, enzalutamide, apalutamide, daralutamide); **NOTE:** if patient currently on a second generation androgen inhibitor, they must be willing and able to undergo a 2-week washout of the drug prior to day 1 of treatment.
    b. Prior chemotherapy is allowed when administered in the metastatic hormone-sensitive prostate cancer setting. In addition, up to one line of chemotherapy is allowed in the mCRPC setting.
    c. Prior treatment with sipuleucel-T, radium-223, or other non-chemotherapy based treatments for mCRPC (e.g., olaparib, pembrolizumab) is allowed.
11. Recovery from recent surgery, radiotherapy,chemotherapy or other anti-cancer treatment to baseline or ≤ Grade 1 (other than alopecia)
12. Demonstrate adequate organ function as defined in the table below; all Screening labs to be obtained within 28 days prior to day 1 of treatment.

System	**Laboratory Value**
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1,000/μL
Platelet Count	≥ 100,000/μL (without transfusion support in prior 2 weeks)
Hemoglobin (Hgb)	≥ 8 g/dL (**NOTE:** without transfusion support in the prior month)
Renal	
Serum creatinine **OR** Creatinine clearance (CrCl)	≤ 2 × upper limit of normal (ULN) **OR** ≥ 40 mL/min as estimated by the Cockcroft and Gault formula[1] in subjects with creatinine > 2 X ULN

Hepatic	
Bilirubin	≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 x ULN
Aspartate aminotransferase (AST)	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Alanine aminotransferase (ALT)	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Other	
Serum potassium	Within normal limits (**NOTE**: supplementation to achieve this allowed)
Serum albumin	≥ 3 g/dL
[1]See formula in Appendix 2	

13. Patients who have not undergone a bilateral orchiectomy and have a female partner of childbearing potential must use an adequate barrier method of contraception during study treatment and for 90 days after receiving the last dose of CPI-1205.
14. [redacted]
15. Ability to swallow and retain oral medications
16. Ability to understand and willingness to sign an IRB approved written informed consent form (ICF) and authorization permitting release of personal health information including genetic testing relevant to cancer.
17. Able to comply with study visit schedule and assessments

3.3 Exclusion Criteria for Phase 1b Dose Escalation

Patients who meet any of the following criteria will not be enrolled in the study:

1. Known symptomatic brain metastases (**NOTE:** patients with treated epidural disease are allowed)
2. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of treatment (**NOTE**: patients must also meet inclusion criterion #11):
    a. First generation: AR antagonists (e.g., bicalutamide, nilutamide, flutamide) within 4 weeks
    b. 5 alpha reductase inhibitors, ketoconazole, estrogens (including diethylstilbesterol [DES]), or progesterones within 2 weeks
    c. Chemotherapy within 3 weeks
    d. Biologic therapy within 4 weeks

   e. Investigational therapy within 3 weeks (or within a time interval less than at least 5 half-lives of the investigational agent [if known], whichever is longer).
   f. Immunotherapy within 4 weeks
   g. Radionuclide therapy within 4 weeks
3. Radiation therapy for the treatment of metastasis within 1 week prior to day 1 of treatment (**NOTE**: a single fraction of radiotherapy for palliation confined to one field **IS** permitted within 1 week prior to day 1 of treatment)
4. Herbal products that may decrease PSA levels within 4 weeks prior to day 1 of treatment
5. Systemic steroids greater than 10 mg of prednisone/prednisolone per day within 4 weeks prior to day 1 of treatment (**NOTE:** see Section 6.3.2.5)
6. Major surgery within 4 weeks prior to day 1 of treatment
7. Planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery
8. Structurally unstable bone lesions concerning for impending fracture
9. Clinically significant cardiovascular disease including:
   a. Myocardial infarction (MI)/Stroke within 6 months prior to day 1 of treatment
   b. Uncontrolled angina within 3 months
   c. Congestive heart failure (CHF) with New York Heart Association (NYHA; see Appendix 3) class 3 or 4
   d. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
   e. Uncontrolled hypertension (systolic blood pressure (BP) > 170 mmHg or diastolic BP > 105 mmHg at screening) despite two concomitant antihypertensive therapies
   f. QT interval corrected by the Fridericia correction formula (QTcF) >500 msec on the screening ECG
10. Active or symptomatic viral hepatitis or chronic liver disease
11. History of unresolved adrenal dysfunction
12. GI disorder that negatively affects absorption
13. Required treatment with one of the prohibited concomitant medications;**see Section 6.3 and Appendix 4**; **NOTE: each patient's list of concomitant medications MUST be checked against the list of prohibited concomitant medications in Appendix 4.**
14. Achlorhydria, either documented or suspected on the basis of an associated disease (e.g., pernicious anemia, atrophic gastritis, or certain gastric surgical procedures)
15. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within 12 months prior to day 1 of treatment, cerebral vascular accident or brain arteriovenous malformation
16. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ bladder cancer, or other cancer for which the patient has been disease-free for at least two years

17. Any other concurrent severe and/or uncontrolled concomitant medical condition that could compromise participation in the study (e.g., clinically significant pulmonary disease, clinically significant psychiatric or neurological disorder, active or uncontrolled infection)
18. Patient unwilling or unable to comply with this study protocol

3.4 Inclusion Criteria for Phase 1b HPEC(s)

Patients must meet all of the following criteria to be enrolled in this study:

1. Age ≥ 18 years
2. ECOG performance status 0-1 (see Appendix 1); **NOTE**: performance status must be documented by 2 independent evaluators.
3. Life expectancy of at least 12 weeks
4. Histologically or cytologically confirmed adenocarcinoma of the prostate; **NOTE**: pure small cell carcinoma is excluded.
5. Documented metastatic disease.
6. At least one measurable lymph node per PCWG3 (see Section 10.2.1)
7. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue GnRH analog or antagonist (medical castration)
8. Serum testosterone <50 ng/dL
9. Progressive disease in the setting of medical or surgical castration (i.e., CRPC) as assessed by the investigator and that includes at least one of the following:
    a. Evidence of progression as measured by PSA defined as: PSA ≥ 2 ng/mL (or PSA ≥ 1 ng/mL if PSA progression is the only manifestation of progressive disease) and rising PSA by at least 2 consecutive measurements a minimum of 1-week apart **AND/OR**
    b. Soft tissue disease progression as per RECIST 1.1 [74] **AND/OR**
    c. Bone disease progression defined by two or more new lesions on bone scan
10. Prior treatment:
    a. Only one prior line of a second generation androgen inhibitor from a different class than the one chosen for the applicable phase 2 study (the 2 classes are CYP17 inhibitors [e.g., abiraterone, orteronel] and AR inhibitors [e.g., enzalutamide, apalutamide]). Patient must have progressed after ≥ 24 weeks of treatment with this second generation angrogen inhibitor. **NOTE:** if patient currently on a second generation androgen inhibitor, they must be willing and able to undergo a 2-week washout of the drug prior to day 1 of treatment. **NOTE:** patient must not have evidence of anti-androgen withdrawal syndrome during washout.
    b. The last second generation androgen inhibitor treatment received must not be from the same class as that incorporated in the applicable HPEC; i.e., if the HPEC

incorporates enzalutamide, the last second generation androgen inhibitor therapy cannot be enzalutamide, apalutamide, etc.

c. Prior chemotherapy for mCRPC must have included at least one and no more than two prior lines of taxane-based chemotherapy (**NOTE:** patient must have progressed during at least one line); chemotherapy (including taxane-based) administered in the metastatic hormone-sensitive prostate cancer setting is allowed.
d. Prior treatment with sipuleucel-T, radium-223, or other non-chemotherapy based treatments for mCRPC (e.g., olaparib, pembrolizumab, nivolumab) is allowed.

11. Recovery from recent surgery, radiotherapy, chemotherapy or other anti-cancer treatment to baseline or ≤ Grade 1 (other than alopecia)
12. Demonstrate adequate organ function as defined in the table below; all Screening labs to be obtained within 28 days prior to day 1 of treatment.

System	**Laboratory Value**
Hematological	
ANC	≥ 1,000/μL
Platelet Count	≥ 100,000/μL (without transfusion support in prior 2 weeks)
Hgb	≥ 8 g/dL (without transfusion support in the prior month)
Renal	
Serum creatinine **OR** CrCl	≤ 2 × ULN **OR** ≥ 40 mL/min as estimated by the Cockcroft and Gault formula[1] in subjects with creatinine > 2 X ULN
Hepatic	
Bilirubin	≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 x ULN
AST	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
ALT	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Other	
Serum potassium	Within normal limits (**NOTE**: supplementation to achieve this allowed)
Serum albumin	≥ 3 g/dL
[1]See formula in Appendix 2	

13. Patients who have not undergone a bilateral orchiectomy and have a female partner of childbearing potential must use an adequate barrier method of contraception during study treatment and for 90 days after receiving the last dose of CPI-1205.

14. [redacted]
15. Ability to swallow and retain oral medications
16. Ability to understand and willingness to sign an IRB approved written ICF and authorization permitting release of personal health information including genetic testing relevant to cancer.
17. Able to comply with study visit schedule and assessments

3.5 Exclusion Criteria for Phase 1b HPEC(s)

Patients who meet any of the following criteria will not be enrolled in the study:

1. Known symptomatic brain metastases (**NOTE:** patients with treated epidural disease are allowed)
2. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of treatment (**NOTE**: patients must also meet inclusion criterion #11):
    a. First generation: AR antagonists (e.g., bicalutamide, nilutamide, flutamide) within 4 weeks
    b. 5 alpha reductase inhibitors, ketoconazole, estrogens (including DES), or progesterones within 2 weeks
    c. Chemotherapy within 3 weeks
    d. Biologic therapy within 4 weeks
    e. Investigational therapy within 3 weeks (or within a time interval less than at least 5 half-lives of the investigational agent [if known], whichever is longer).
    f. Immunotherapy within 4 weeks
    g. Radionuclide therapy within 4 weeks
3. Radiation therapy for the treatment of metastasis within 1 week prior to day 1 of treatment (**NOTE**: a single fraction of radiotherapy for palliation confined to one field **IS** permitted within 1 week prior to day 1 of treatment)
4. Herbal products that may decrease PSA levels within 4 weeks prior to day 1 of treatment
5. Systemic steroids greater than 10 mg of prednisone/prednisolone per day within 4 weeks prior to day 1 of treatment (**NOTE:** see Section 6.3.2.5)
6. Major surgery within 4 weeks prior to day 1 of treatment
7. Structurally unstable bone lesions concerning for impending fracture
8. Clinically significant cardiovascular disease including:
    a. MI/Stroke within 6 months prior to day 1 of treatment
    b. Uncontrolled angina within 3 months
    c. CHF with NYHA (see Appendix 3) class 3 or 4
    d. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)

e. Uncontrolled hypertension (systolic BP > 170 mmHg or diastolic BP > 105 mmHg at screening) despite two concomitant antihypertensive therapies
f. QTcF >500 msec on the screening ECG

9. Active or symptomatic viral hepatitis or chronic liver disease
10. History of unresolved adrenal dysfunction
11. GI disorder that negatively affects absorption
12. Required treatment with one of the prohibited concomitant medications; **see Section 6.3 and Appendix 4; NOTE: each patient's list of concomitant medications MUST be checked against the list of prohibited concomitant medications in Appendix 4.**
13. Achlorhydria, either documented or suspected on the basis of an associated disease (e.g., pernicious anemia, atrophic gastritis, or certain gastric surgical procedures)
14. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within 12 months prior to day 1 of treatment, cerebral vascular accident or brain arteriovenous malformation
15. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ bladder cancer, or other cancer for which the patient has been disease-free for at least two years
16. Any other concurrent severe and/or uncontrolled concomitant medical condition that could compromise participation in the study (e.g., clinically significant pulmonary disease, clinically significant psychiatric or neurological disorder, active or uncontrolled infection)
17. Patient unwilling or unable to comply with this study protocol

3.6 Inclusion Criteria for Phase 2

Patients must meet all of the following criteria to be enrolled in this study:

1. Age ≥ 18 years
2. ECOG performance status 0-1 (see Appendix 1)
3. Life expectancy of at least 12 weeks
4. Histologically or cytologically confirmed adenocarcinoma of the prostate. **NOTE**: pure small cell carcinoma is excluded.
5. Documented metastatic disease. **NOTE**: at least 50% of patients in each phase 2 trial opened must have measurable disease (see Section 4.3).
6. Must have undergone bilateral orchiectomy (surgical castration) or be willing to continue GnRH analog or antagonist (medical castration).
7. Serum testosterone <50 ng/dL
8. Progressive disease in the setting of medical or surgical castration (i.e., CRPC) as assessed by the investigator and that includes at least one of the following:
    a. Evidence of progression as measured by PSA defined as: PSA ≥ 2 ng/mL (or PSA ≥ 1 ng/mL if PSA progression is the only manifestation of progressive disease) and rising PSA by at least 2 consecutive measurements a minimum of 1-week apart **AND/OR**

b. Soft tissue disease progression as per RECIST 1.1 **AND/OR**
c. Bone disease progression defined by two or more new lesions on bone scan

9. Bisphosphonate or denosumab therapy allowed provided dose has been stable for ≥ 4 weeks prior to day 1 of treatment.
10. Prior treatment:
    a. Only one prior line of a second generation androgen inhibitor from a different class than the one chosen for the applicable phase 2 study (the 2 classes are CYP17 inhibitors [e.g., abiraterone, orteronel] and AR inhibitors [e.g., enzalutamide, apalutamide]). Patient must have progressed after ≥ 24 weeks of treatment with this second generation angrogen inhibitor. **NOTE:** if patient currently on a second generation androgen inhibitor, they must be willing and able to undergo a 2-week washout of the drug prior to day 1 of treatment. **NOTE:** patient must not have evidence of anti-androgen withdrawal syndrome during washout.
    b. No prior chemotherapy for mCRPC allowed; chemotherapy (including taxane-based) administered in the metastatic hormone-sensitive prostate cancer setting is allowed.
    c. Prior treatment with sipuleucel-T, radium-223, or other non-chemotherapy based treatments approved by the US FDA for the treatment of mCRPC is allowed; prior treatment with non-chemotherapy based treatments that are not approved for the treatment of mCRPC (e.g., pembrolizumab, ipilimumab, olaparib) are not allowed.
11. Recovery from recent surgery, radiotherapy, chemotherapy or other anti-cancer treatment to baseline or ≤ Grade 1 (other than alopecia)
12. Demonstrate adequate organ function as defined below; all screening labs to be obtained within 28 days prior to day 1 of treatment.

System	**Laboratory Value**
Hematological	
ANC	≥ 1,000/μL
Platelet Count	≥ 100,000/μL (without transfusion support in prior 2 weeks)
Hgb	≥ 8 g/dL (**NOTE:** without transfusion support in the prior month)
Renal	
Serum creatinine **OR** CrCl	≤ 2 × ULN **OR** ≥ 40 mL/min as estimated by the Cockcroft and Gault formula[1] in subjects with creatinine > 2 × ULN
Hepatic	
Bilirubin	≤ 1.5 × ULN unless evidence of Gilbert's disease in which case < 3 × ULN
AST	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases

ALT	≤ 2.5 × ULN without liver metastases; must be ≤ 5 × ULN with liver metastases
Other	
Serum potassium	Within normal limits (**NOTE**: supplementation to achieve this allowed)
Serum albumin	≥ 3 g/dL
[1]See formula in Appendix 2	

13. Patients who have not undergone a bilateral orchiectomy and have a female partner of childbearing potential must use an adequate barrier method of contraception during study treatment and for 90 days after receiving the last dose of CPI-1205 (or partner drug in the control arm of any randomized phase 2 trial if the patient does not participate in the crossover).
14. [redacted]
15. Ability to swallow and retain oral medications.
16. Ability to understand and willingness to sign an IRB approved written ICF and authorization permitting release of personal health information including genetic testing relevant to cancer.
17. Able to comply with study visit schedule and assessments.

3.7 Exclusion Criteria for Phase 2

Patients who meet any of the following criteria will not be enrolled in the study:

1. Known symptomatic brain metastases (**NOTE:** patients with treated epidural disease are allowed)
2. Treatment with any of the following for prostate cancer within the indicated timeframe prior to day 1 of treatment (**NOTE**: patients must also meet inclusion criterion #11):
    a. First-generation AR antagonists (e.g., bicalutamide, nilutamide, flutamide) within 4 weeks
    b. 5 alpha reductase inhibitors, ketoconazole, estrogens (including DES), or progesterones within 2 weeks
    c. Chemotherapy within 3 weeks
    d. Biologic therapy within 4 weeks
    e. Radionuclide therapy within 4 weeks
3. Radiation therapy for the treatment of metastasis within 1 week prior to day 1 of treatment (**NOTE**: a single fraction of radiotherapy for palliation confined to one field **IS** permitted within 1 week prior to day 1 of treatment)

4. Herbal products that may decrease PSA levels within 4 weeks prior to day 1 of treatment
5. Systemic steroids greater than 10 mg of prednisone/prednisolone per day within 4 weeks prior to day 1 of treatment (**NOTE:** see Section 6.3.2.5)
6. Major surgery within 4 weeks prior to day 1 of treatment
7. Planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery
8. Structurally unstable bone lesions concerning for impending fracture
9. Clinically significant cardiovascular disease including:
    a. MI/stroke within 6 months prior to day 1 of treatment
    b. Unstable angina within 3 months
    c. CHF with NYHA (see Appendix 3) class 3 or 4
    d. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    e. Uncontrolled hypertension (systolic BP > 170 mmHg or diastolic BP > 105 mmHg at screening) despite two concomitant antihypertensive therapies
    f. QTcF >500 msec on the screening ECG
10. Active or symptomatic viral hepatitis or chronic liver disease
11. History of unresolved adrenal dysfunction
12. GI disorder that negatively affects absorption
13. Required treatment with one of the prohibited concomitant medications; **see Section 6.3 and Appendix 4; NOTE: each patient's list of concomitant medications MUST be checked against the list of prohibited concomitant medications in Appendix 4.**
14. Achlorhydria, either documented or suspected on the basis of an associated disease (e.g., pernicious anemia, atrophic gastritis, or certain gastric surgical procedures)
15. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within 12 months prior to day 1 of treatment, cerebral vascular accident or brain arteriovenous malformation
16. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ bladder cancer, or other cancer for which the patient has been disease-free for at least two years
17. Any other concurrent severe and/or uncontrolled concomitant medical condition that could compromise participation in the study (e.g., clinically significant pulmonary disease, clinically significant psychiatric or neurological disorder, active or uncontrolled infection)
18. Patient unwilling or unable to comply with this study protocol

4 ENROLLMENT

A patient is considered to be enrolled in the study once written informed consent to study participation has been obtained, all eligibility criteria have been met, and the completed enrollment form has been sent to study contract research organization (CRO), signed by the appropriate representative, and returned to the investigational site.

Procedures for completion of enrollment information will be described in the study manual.

4.1 Patient numbering

Each patient in the study is identified by a unique **patient number.** The unique patient number is a combination of his **study center number** and **a second number reflecting the sequence of patient enrollment.** The study center number is assigned by Constellation Pharmaceuticals to each investigative site.

The procedures for patient numbering and cohort coordination between the study sites will be provided in a separate document prior to study start.

Informed consent must be obtained before performing any study-specific test to assess a patient's eligibility for this study.

4.2 Treatment assignment: Phase 1b

The assignment of a patient to a given dose cohort during dose escalation and/or to the HPEC(s) will be coordinated by Constellation Pharmaceuticals, and will take prior history of treatment with chemotherapy, abiraterone, enzalutamide and/or other second generation androgen inhibitor, concomitant medications, availability of open slots within each cohort, etc. into account.

4.3 Treatment assignment: Phase 2

For the randomized phase 2 study(ies), at the end of the screening period, eligible patients will be randomly assigned in a 1:1 ratio to the combination arm (CPI-1205 at the RP2D [with or without cobicistat] in combination with enzalutamide or abiraterone/prednisone) or the control arm (enzalutamide or abiraterone/prednisone as monotherapy).

Patients must start study treatment within 3 days of randomization; if not, the Sponsor must be notified. Randomization will be stratified by measurable disease status (yes vs no) and CTC status (favorable vs unfavorable). An interactive response technology (IRT) system will be used to manage the randomization process.

If a single arm phase 2 study is conducted, all patients will receive the combination of CPI-1205 at the RP2D (with or without cobicistat) in combination with enzalutamide or abiraterone/prednisone.

NOTE: at least 50% of patients in any phase 2 trial opened must have measurable soft tissue disease. Therefore, measurable disease may become an eligibility requirement during the course of enrollment if the number of patients with measurable disease is insufficient.

4.4 Treatment blinding

This is an open-label study, and treatment blinding is not applicable.

5 STUDY DESIGN

5.1 Overview of Study Design

This is a phase 1b/2, multi-center, open-label study of CPI-1205 alone and with cobicistat in patients with mCRPC in combination with either enzalutamide or abiraterone/prednisone.

During phase 1b dose escalation and prior to Amendment 2, patients were enrolled into phase 1b Dose Level 1A (CPI-1205 PO TID + enzalutamide or abiraterone/prednisone). As of Amendment 2, new patients will be enrolled into cohorts including 1) dose escalating CPI-1205 PO BID + fixed dose cobicistat PO BID + enzalutamide and 2) dose escalating CPI-1205 PO BID + fixed dose cobicistat PO BID + abiraterone/prednisone. Based on emerging data, the SSC (see Section 5.4.7) may elect to add additional patients to cohort 1A and/or to cohort (-)1A, and to determine an MTD for CPI-1205 PO TID. [redacted]

As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population. A HPEC may begin enrollment if [redacted] or [redacted] patients treated with a specific regimen (i.e., CPI-1205 with or without cobicistat, in combination with enzalutamide or abiraterone) at a given dose level during phase 1b dose escalation experience a DLT. **NOTE:** the SSC will recommend which regimen(s) and dose to evaluate in the HPEC(s) based on safety, PK, efficacy, etc. **NOTE:** a Simon's 2-stage design will be used for any HPEC that opens. After enrollment of [redacted] patients (stage 1), the SSC will recommend whether to continue to stage 2 at the current dose and schedule based on efficacy, [redacted] based on safety, PK, efficacy, etc.

Following determination of the MTD in each of the CPI-1205 BID + cobicistat combinations (and possibly in the CPI-1205 TID combination) and after evaluation of the BID cohorts without cobicistat (if applicable) during phase 1b dose escalation, only one of the CPI-1205 dosing schedules will be selected as the RP2D for each combination (i.e., with enzalutamide and with abiraterone/prednisone). One or both of the combinations may proceed to phase 2 after consideration of PK and pharmacodynamic results, data from the HPEC(s) and safety data. **NOTE:** [redacted] Throughout phase 1b (all cohorts), safety oversight will be provided by the SSC comprised of study investigators, the medical monitor (or external medical representative of the Sponsor), and the Sponsor.

[redacted]

CPI-1205 will be given orally by mouth (PO) TID or BID (as of Amendment 2), cobicistat dosing will begin with one dose the evening prior to day 1 of CPI-1205 (i.e., the evening of day 0), and then continue PO BID starting on day 1 of CPI-1205, enzalutamide and abiraterone will be given PO once daily, and prednisone will be given PO BID (or with frequency of prednisone at the discretion of the investigator). Rules regarding administration of each agent with or without food is outlined in Section 6.1. In addition, classes of concomitant drugs that are prohibited or to be used with caution are outlined in Section 6.3.

Successive 28-day cycles of treatment will be repeated, without planned breaks in dosing, as long as the respective combination is well tolerated until radiographic disease progression (as determined by the investigator), unequivocal clinical progression or a SRE (see Section 10 for definitions) **AND** planned initiation of another systemic treatment for prostate cancer. Prostate cancer is heterogeneous, and patients with confirmed disease progression in one tumor site may have other lesion(s) that could benefit from continued treatment. Given the paucity of other effective treatment options, investigators may elect to continue patients with radiographic disease progression, unequivocal clinical progression or a SRE who will not be starting another systemic treatment on study treatment. When patients in the control arm of any randomized phase 2 trial conducted experience radiographic disease progression (as determined by the investigator), unequivocal clinical progression or an SRE, patients will have the option to cross over to the combination arm (i.e., continue on the second generation androgen inhibitor and add CPI-1205 [with or without cobicistat] provided they meet the required criteria as outlined in Section 5.5.1 and once the decision is made to initiate another systemic therapy for prostate cancer. Treatment will again continue in 28-day cycles until unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE **AND** planned initiation of other systemic treatment for prostate cancer or until unacceptable toxicity.

NOTE: At the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE, patients enrolled in Dose Level 1A who receive CPI-1205 PO TID without cobicistat may have the option to switch to CPI-1205 PO BID with cobicistat at the discretion of the investigator, and only after consultation with the Medical Monitor. See Section 5.4.9.

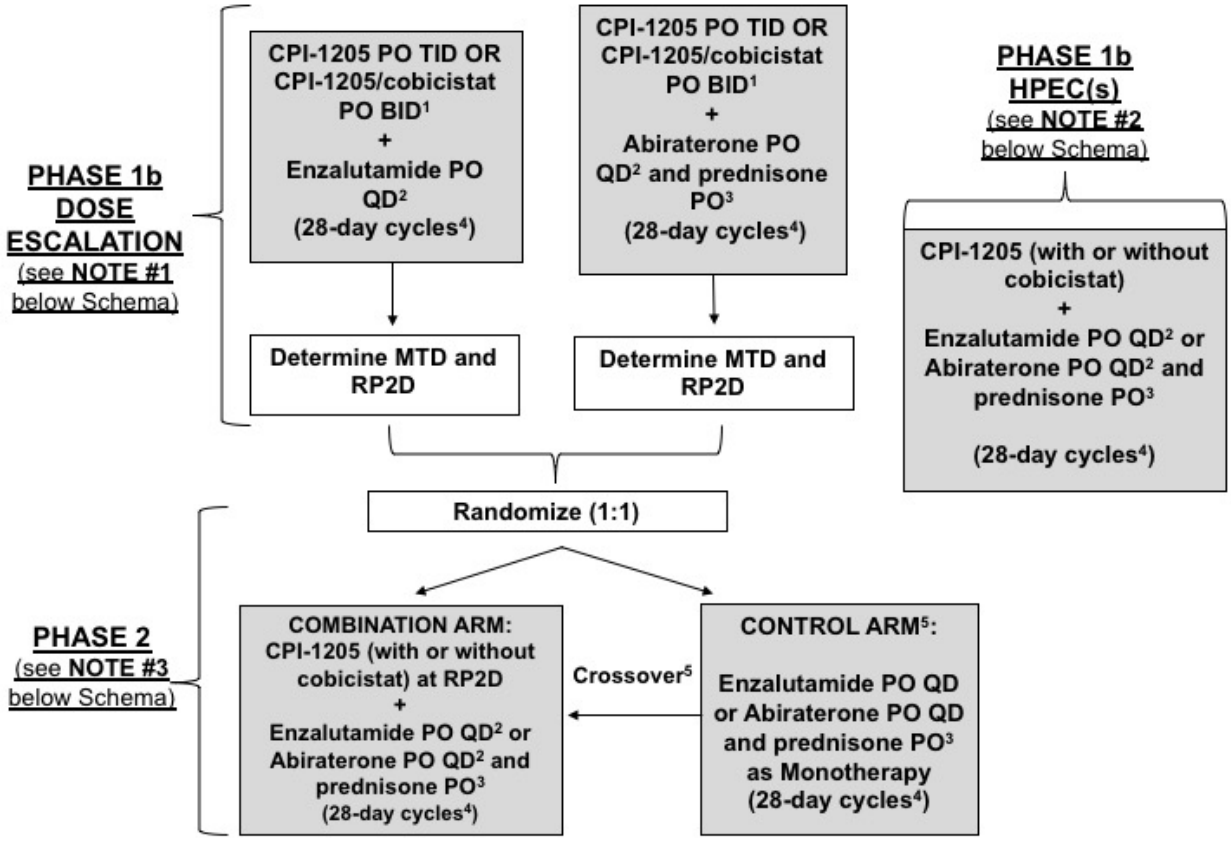
NOTE: PSA rise without evidence of radiographic progression, unequivocal clinical progression or without a SRE will not be a criterion to start a new systemic anti-neoplastic therapy throughout the study.

NOTE: Patients who have not undergone surgical castration must continue their medical castration, i.e., GnRH analog or antagonist, for the duration of study treatment.

NOTE: For the HPEC(s) and for any phase 2 study conducted, sites will be required to submit all radiographic imaging for CRR. Details on the CRR will be provided in a CRR charter, provided as a document separate from the protocol.

5.2 Schema

Figure 5-1 Study Design Schematic



BID=twice daily; TID=three times daily; QD=once daily; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose; HPEC=heavily pretreated expansion cohort

[1]See Sections 5.4.1 and 5.4.2 for doses to be administered within each cohort
[2]In combination arms, dose of enzalutamide and/or abiraterone may be increased after Cycle 2 based on the specific patient's PK and only after consultation with the Medical Monitor. **NOTE:** If abiraterone increased it may be given PO BID. See Sections 6.2.3 and 6.2.5.
[3]Frequency of prednisone at the discretion of the investigator
[4]Repeat 28-day cycles until radiographic disease progression (as determined by the investigator), unequivocal clinical progression or SRE AND planned initiation of other systemic treatment for prostate cancer
[5]At the time of radiographic progression (as determined by the investigator), unequivocal clinical progression or SRE, control arm patients may be eligible to cross over to combination arm if they meet eligibility as outlined in Section 5.5.1.

NOTE #1: See Section 5.1 regarding TID cohort already enrolled during phase 1b dose escalation; as of Amendment 2, new cohorts of patients will enroll into BID cohorts; dose escalation of each BID regimen to occur simultaneously.

NOTE #2: As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population. A HPEC may begin enrollment if [redacted] or [redacted] patients treated with a specific regimen (i.e., CPI-1205 with or without cobicistat, in combination with enzalutamide or abiraterone) at a given dose level during phase 1b dose escalation experience a DLT. The SSC will recommend which regimen(s) and dose to evaluate in the HPEC(s) based on safety, PK, efficacy, etc. **NOTE:** a Simon's 2-stage design will be used for any HPEC that opens. After enrollment of 9 patients (stage 1), the SSC will recommend whether to continue to stage 2 at the current dose and schedule based on efficacy, or whether a change in CPI-1205 schedule (e.g., from TID without cobicistat to BID with cobicistat) is warranted based on safety, PK, efficacy, etc.

[redacted]

5.3 Number of Patients

The number of patients in phase 1b dose escalation will depend on safety, but could range from approximately [redacted] per combination (including patients from the CPI-1205 TID and CPI-1205 BID with cobicistat cohorts). Approximately [redacted] evaluable patients will be enrolled in any Simon's 2 stage design for any phase 1b HPEC that opens. The number of patients in phase 2 will depend on whether 1 or 2 randomized trials are conducted. Any randomized trial that is opened will enroll approximately [redacted] evaluable patients ([redacted] patients per arm). Any single arm trial will enroll up to [redacted] evaluable patients. Additional patients may be enrolled if more dose levels have to be evaluated to determine the MTD or RP2D, if a dose cohort is expanded or for the replacement of non-evaluable patients.

5.4 Phase 1b

5.4.1 Dose Levels for CPI-1205 (with and without Cobicistat) + Enzalutamide during Phase 1b Dose Escalation

Table 5-1 Dose Levels for CPI-1205 (with and without Cobicistat) + Enzalutamide

[redacted]	**Enzalutamide[e]**
[redacted]	160mg PO once daily (4 x 40mg capsules)
[redacted]	160mg PO once daily (4 x 40mg capsules)
[redacted]	160mg PO once daily (4 x 40mg capsules)
[redacted]	160mg PO once daily (4 x 40mg capsules)
[redacted]	160mg PO once daily (4 x 40mg capsules)

[a]Prior to Amendment 2, a cohort of CPI-1205 TID (without cobicistat) was enrolled into Dose Level 1A. This cohort of patients will continue CPI-1205 PO TID without cobicistat. [redacted]

[b]Cohort 1B will start to enroll patients as of Amendment 2.

[c]Cobicistat dosing will start the evening before day 1 of CPI-1205 (i.e., on the evening of day 0). Cobicistat dosing will then continue BID starting on day 1 of CPI-1205. See Section 6.1 for rules regarding drug administration with food.

[d]Dose will be determined based on results from Cohort 1B in consultation with the SSC.

[redacted]

5.4.2 Dose Levels for CPI-1205 (with and without Cobicistat) + Abiraterone/Prednisone during Phase 1b Dose Escalation

Table 5-2 Dose Levels for CPI-1205 (with and without Cobicistat) + Abiraterone/Prednisone

	Abiraterone[f]	Prednisone
[redacted]	1000mg PO once daily (4 x 250mg tablets)	5mg PO BID[a]
	1000mg PO once daily (4 x 250mg tablets)	5mg PO BID[a]
	1000mg PO once daily (4 x 250mg tablets)	5mg PO BID[a]
	1000mg PO once daily (4 x 250mg tablets)	5mg PO BID[a]
	1000mg PO once daily (4 x 250mg tablets)	5mg PO BID[a]

[a]Or frequency of prednisone dose at discretion of investigator

[b]Prior to Amendment 2, a cohort of CPI-1205 TID (without cobicistat) was enrolled into Dose Level 1A. This cohort of patients will continue CPI-1205 PO TID without cobicistat. The SSC may elect to add additional patients to the TID cohorts, and to determine an MTD for CPI-1205 PO TID without cobicistat, based on emerging data from all cohorts. [redacted]

[c]Cohort 1B will start to enroll patients as of Amendment 2.

[d]Cobicistat dosing will start the evening before day 1 of CPI-1205 (i.e., on the evening of day 0). Cobicistat dosing will then continue BID starting on day 1 of CPI-1205. See Section 6.1 for rules regarding drug administration with food.

[e] Dose will be determined based on results from Cohort 1B in consultation with the SSC. [redacted]

5.4.3 Dose Escalation Guidelines

During phase 1b dose escalation and prior to Amendment 2, patients were enrolled into phase 1b Dose Level 1A (CPI-1205 PO TID + enzalutamide or abiraterone/prednisone). As of Amendment 2, new patients will be enrolled into cohorts of increasing doses of CPI-1205 PO BID with fixed doses of cobicistat PO BID plus either enzalutamide or abiraterone/prednisone (depending on which combination the patient is assigned to) until the MTD is determined. [redacted]

[redacted] This decision will be based on emerging safety, PK, pharmacodynamic and efficacy data from all cohorts. Evaluable patients are patients who meet the minimum treatment and safety evaluation requirements of the study (see Section 5.6.1) and/or who experience a DLT during Cycle 1.

The dose of CPI-1205 will not be adjusted for body weight or body surface area; all patients treated in the same cohort/at the same dose level will receive the same total milligram dose of CPI-1205 per day.

5.4.3.1 Phase 1b (Dose Level 1A and [-]1A Cohorts, i.e., CPI-1205 PO TID without Cobicistat)

For each combination the following rules apply (if at least 6 patients are enrolled in Dose Level 1A):

The first patients will be enrolled into the Dose Level 1A cohort.

- If no more than [redacted] experiences a DLT among [redacted] evaluable patients in the Dose Level 1A cohort, this cohort will be considered safe.
- If [redacted] patients experience a DLT among [redacted] evaluable patients in the Dose Level 1A cohort, the SSC, (see Section 5.4.7) may elect to accrue 6 more patients at the same dose level. Alternatively, 6 patients may be enrolled in the Dose Level (-)1A cohort.
- If more than [redacted] patients experience a DLT among [redacted] evaluable patients in the Dose Level 1A cohort, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded. [redacted] patients may be enrolled in the Dose Level (-)1A cohort.

NOTE: Intra-patient dose escalation of CPI-1205 is not allowed.

NOTE: As of Amendment 2, new patients will be enrolled into CPI-1205 BID cohorts with cobicistat. The SSC may elect to add additional patients to cohort 1A and/or to cohort (-)1A, and to determine an MTD for CPI-1205 PO TID based on emerging data from the cobicistat cohorts.

5.4.3.2 Phase 1b (Dose Level 1B, 2B and [-]1B Cohorts, i.e., CPI-1205 PO BID with Cobicistat)

The dose escalation within each combination will proceed as follows:

The firs [redacted] patients will be enrolled in the Dose Level 1B cohort.

- If [redacted] valuable patients in the Dose Level 1B cohort experiences a DLT, the next [redacted] patients will be assigned to the Dose Level 2B* cohort.
- If [redacted] evaluable patients in the Dose Level 1B cohort experiences a DLT, then [redacted] additional patients will be enrolled at the same dose level.

- If [redacted] of the additional patients (i.e., [redacted] evaluable patients in the Dose Level 1B cohort) experiences a DLT, the next [redacted] patients will be assigned to the Dose Level 2B* cohort.
- If [redacted] of the additional patients (i.e., [redacted] evaluable patients in the Dose Level 1B cohort) experiences a DLT, the MTD will have been exceeded and the next [redacted] will be enrolled into the Dose Level (-)1B cohort.

- If [redacted] evaluable patients in the Dose Level 1B cohort experiences a DLT, the MTD will have been exceeded and the next [redacted] patients will be enrolled into the Dose Level (-)1B cohort.

* The dose of CPI-1205 (600 or 800mg PO BID) will be determined based on results from the Dose Level 1B cohort in consultation with the SSC.

If the Dose Level 2B cohort opens:

- If [redacted] evaluable patients in the Dose Level 2B cohort experiences a DLT, this cohort will be considered safe.
- If [redacted] evaluable patients in the Dose Level 2B cohort experiences a DLT, then [redacted] will be enrolled at the same dose level.
  - If [redacted] of the additional patients (i.e., [redacted] evaluable patients in the Dose Level 2B cohort) experiences a DLT, this cohort will be considered safe.
  - If [redacted] of the additional patients (i.e., [redacted] evaluable patients in the Dose Level 2B cohort) experiences a DLT, the MTD will have been exceeded and additional patients may be enrolled into the Dose Level 1B cohort* (unless [redacted] patients have already been enrolled).
- If [redacted] evaluable patients experience a DLT, the MTD will have been exceeded and additional patients may be enrolled into the Dose Level 1B cohort* (unless [redacted] patients have already been enrolled).

[redacted]

NOTE: Dose escalation beyond Dose Level 2B is not allowed.

[redacted]

[redacted]

5.4.4 MTD

The MTD will be determined for CPI-1205 PO BID with cobicistat for each combination. The SSC may also elect to determine the MTD for CPI-1205 PO TID. [redacted] The MTD will not be determined until all patients entered into the cohort under evaluation have either completed Cycle 1 or experienced a DLT.

5.4.5 RP2D

Only one of the CPI-1205 dosing schedules will be selected as the RP2D for each combination. The RP2D will be selected based on PK and overall tolerability data (i.e., DLT, cumulative and/or delayed toxicity that limits dosing) from all patients treated at different dose levels in this study and will not exceed the MTD.

5.4.6 Definition of Dose-Limiting Toxicities

DLT is defined as an AE or abnormal laboratory value that meets any of the criteria listed below in Table 5-3 and where a relationship to the investigational agent (CPI-1205 alone or when given with cobicistat) cannot be ruled out. Toxicities will be graded according to the NCI CTCAE v4.03. See Section 6.3.5 for management of and supportive care for any treatment related toxicities (including DLT).

For the purpose of making dose escalation decisions all DLTs occurring during the first cycle of treatment with CPI-1205 (with or without cobicistat) must be included.

Table 5-3 Definitions of Dose-Limiting Toxicities

Toxicity	Any of the following:
Hematology	Grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting >7 days
	Febrile neutropenia of any duration (ANC < 1.0 x 10^9/Land single oral temperature >38.3°C or ≥ 38°C for >1 hour)
	Grade 4 thrombocytopenia (platelets < 25 x 10^9/L) of any duration
	Grade 3 thrombocytopenia (platelets between 25-49 x 10^9/L) with bleeding or any requirement for platelet transfusion
Hepatic	≥ Grade 3 total bilirubin (except Gilbert's disease)
	≥ Grade 3 ALT/AST lasting >7 days in patients who enroll with ≤ Grade 1 ALT/AST
	Tripling of ALT/AST lasting >7 days in patients who enroll with Grade 2 ALT/AST

Toxicity	Any of the following:
	ALT/AST > 3 x ULN (i.e., ≥ Grade 2) with bilirubin > 2 x ULN without another explanation (e.g., cholestasis) in patients who enroll with ≤ Grade 1 ALT/AST
	Doubling of ALT/AST with bilirubin > 2 x ULN without another explanation (e.g., cholestasis) in patients who enroll with Grade 2 ALT/AST
Metabolic	≥ Grade 3 electrolyte disturbance of >72 hours (supplementation allowed)
Gastrointestinal	≥ Grade 3 vomiting or Grade 3 nausea of >72 hours duration in spite of optimal anti-emetic supportive care
	≥ Grade 3 diarrhea of >72 hours duration in spite of optimal anti-diarrheal supportive care
Other	Grade 3 fatigue lasting >72 hours
	Other CPI-1205-related non-hematologic toxicities ≥ Grade 2 that, in the opinion of the investigator, require dose reduction or discontinuation of treatment with CPI-1205
	<75% of total doses within Cycle 1 (i.e., < 63 doses) are taken for reasons related to CPI-1205 toxicity
	Other toxicities may be considered a DLT as determined by the Investigator in conjunction with the SSC

5.4.7 Phase 1b HPEC(s)

As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population. To be included in the HPEC(s), patients must have had prior treatment with and progressed on chemotherapy in the mCRPC setting, and must have been treated with and progressed on two lines of a second generation androgen inhibitor (one from each class). The last second generation androgen inhibitor treatment received must not be from the same class as that incorporated in the applicable HPEC; i.e., if the HPEC incorporates enzalutamide, the last second generation androgen inhibitor therapy cannot be enzalutamide, apalutamide, etc. Patients must also have at least one measurable lymph node.

A HPEC may begin enrollment if [redacted] patients treated with a specific regimen (i.e., CPI-1205 with or without cobicistat, in combination with enzalutamide or abiraterone) at a given dose level during phase 1b dose escalation experience a DLT. **NOTE:** the SSC will recommend decide which regimen(s) and dose to evaluate in the HPEC(s) based on safety, PK, efficacy, etc. **NOTE:** a Simon's 2-stage design will be used for any HPEC that opens. After enrollment of [redacted] patients (stage 1), the SSC will recommend whether to continue to stage 2 at the current dose and schedule based on efficacy, or whether a change in CPI-1205 schedule (e.g., from TID without cobicistat to BID with cobicistat) is warranted based on safety, PK, efficacy, etc. If the schedule is changed, a new Simon's 2-stage design will be followed.

5.4.7.1 Dose/Schedule of Enzalutamide (if applicable)

If an enzalutamide HPEC is opened, enzalutamide 160mg PO once daily will be administered as 4 x 40mg capsules as per enzalutamide prescribing information for treatment of mCRPC.*

[redacted]

5.4.7.2 Dose/Schedule of Abiraterone/Prednisone (if applicable)

If an abiraterone/prednisone HPEC is opened, abiraterone 1000mg PO once daily will be administered as 4 x 250mg tablets as per abiraterone prescribing information for treatment of mCRPC.* Prednisone will also be administered at a dose of 5mg PO BID (or at another frequency of administration at discretion of the investigator).

[redacted]

5.4.8 Study Safety Committee (SSC)

Throughout phase 1b (all cohorts), safety oversight will be provided by the SSC comprised of study investigators, the medical monitor (or external medical representative of the Sponsor), and the Sponsor. During phase 1b dose escalation, cohort review teleconferences with the SSC will be scheduled approximately one week after the last patient in any cohort completes 28 days of dosing to determine if the next highest dose cohort should be opened. For decisions related to dose escalation and determination of MTD, the incidence of DLTs occurring during the first 28 days (Cycle 1) of CPI-1205 (with or without cobicistat) treatment will be considered. AEs that that would qualify as a DLT but occur after 28 days will be discussed by the SSC to determine if additional action is required, and may be used for determination of the RP2D.

Specifically, the SSC will:

- Review all relevant safety findings including DLTs;
- During phase 1b dose escalation, determine all cohort dose escalation, dose expansion and de-escalation decisions;
- Recommend the regimen(s) and dose to evaluate in phase 1b HPEC(s);
- Recommend whether a CPI-1205 schedule change is warranted after the first stage in phase 1b HPEC(s);
- Determine what additional action is required for AEs that that would qualify as a DLT but occur after 28 days;

- Recommend the RP2D to be used during phase 2.

5.4.9 Continued Treatment after Progression in Cohort 1A

At the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE, patients enrolled in Dose Level 1A who receive CPI-1205 PO TID without cobicistat may have the option to switch to CPI-1205 PO BID with cobicistat at the discretion of the investigator, and only after consultation with the Medical Monitor. Increased exposure to CPI-1205 due to the addition of cobicistat may enable patients to overcome their resistance to treatment.

The decision on the dose of CPI-1205 for the PO BID schedule will be made by the Medical Monitor and will be based on current data from existing BID cohorts (the cobicistat dose will be fixed at 150mg PO BID). Patients will continue to receive the same second generation androgen inhibitor they were on prior to the switch. After patients switch to the CPI-1205/cobicistat BID treatment schedule, they will be followed as per the Schedule of Events in Table 7-4 (i.e., they will follow the same schedule as outlined for phase 2 patients who cross over from the control arm to the combination arm [see Section 5.5.1]).

5.5 Phase 2

Once the MTD/RP2D of CPI-1205 (with or without cobicistat) when combined with enzalutamide and with abiraterone/prednisone is determined in phase 1b dose escalation, additional patients with mCRPC may be enrolled and treated at the RP2D during phase 2 to further evaluate safety and to evaluate efficacy of CPI-1205 (with or without cobicistat) in combination with enazalutamide and/or abiraterone/prednisone.

One or both of the combinations may proceed to phase 2 after consideration of PK and pharmacodynamic results, data from the HPEC(s) and safety data. [redacted] During phase 2, enrollment will be limited to patients [redacted]neration androgen inhibitor (from a different class than the agent chosen for the applicable phase 2 study), who progressed after at least 24 weeks of treatment with the second generation androgen inhibitor, and who have not received prior chemotherapy for mCRPC. In addition, at least 50% of patients enrolled in any phase 2 trial that is opened must have measurable soft tissue disease. [redacted]

[redacted]

5.5.1 Crossover to Combination Arm in Randomized Phase 2

When patients in the control arm of any randomized phase 2 trial conducted experience radiographic disease progression (as determined by the investigator), unequivocal clinical progression or a SRE (see Section 10 for definitions) patients will have the option to cross over to the combination arm (i.e., continue on the second generation androgen inhibitor and add CPI-1205/cobicistat) if eligible to participate, once the decision is made to initiate another systemic therapy for prostate cancer.

Patients will be eligible to start treatment with the combination provided the patient:

- has recovered from any toxicity experienced during the control arm treatment to baseline or ≤ Grade 1
- demonstrates adequate organ function as defined in Phase 2 Inclusion Criterion #12.
- has an ECOG performance status ≤ 1

NOTE: Treatment with the second generation androgen inhibitor may continue while patient is under evaluation for crossover eligibility. **NOTE:** At the time any patient crosses over from the control arm to the combination arm, the first cycle of combination treatment will be considered Cycle 1. Treatment will again continue in 28-day cycles until unequivocal clinical progression, radiographic disease progression (as determined by investigator) or SRE **AND** planned initiation of other systemic treatment for prostate cancer or until unacceptable toxicity.

5.6 Patient Replacement

5.6.1 Phase 1b Dose Escalation

During phase 1b dose escalation, the minimum treatment and safety evaluation requirements are met if, in Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the combination), is observed for ≥ 28 days following the first dose, and is considered by the SSC to have sufficient safety data available to conclude that a DLT did not occur. Patients who do not meet these minimum treatment and safety evaluation requirements and who do not experience DLT will be replaced with new patients if the minimum evaluable patients required per dose level has not been satisfied. **NOTE**: If a patient misses >25% of doses in Cycle 1 for reasons not related to toxicity, the patient can be replaced. If a patient misses >25% of doses in Cycle 1 for reasons related to toxicity, this will be considered a DLT (see Section 5.4.6), and the patient cannot be replaced.

5.6.2 Phase 1b expansion HPEC(s)

A patient enrolled in a phase 1b HPEC is evaluable for the primary endpoint of objective response if:

- In Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the regimen)

- He has at least one post-baseline imaging assessment

Patients who are not evaluable for objective response will be replaced. **NOTE:** all patients enrolled in a HPEC must have at least one measurable lymph node at study entry.

5.6.3 Randomized Phase 2

Any randomized phase 2 trial will be analyzed based on a modified intent-to-treat (mITT) population, which is defined as all randomized patients with at least 1 dose of study treatment and at least one efficacy assessment. Patients who do not meet the criteria for being in the mITT population will be replaced.

5.6.4 Single Arm Phase 2

If a single arm phase 2 study is conducted, a patient is evaluable for the primary endpoints if:

- In Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the combination selected for the study)

- He has at least one post-baseline PSA measurement (for patients evaluable for PSA 50% response)

- He has at least one post-baseline CTC assessment (for patients with ≥ 5 CTCs)

- He has at least one post-baseline imaging assessment (for patients with measurable disease)

Patients who are not evaluable for the primary endpoints will be replaced.

6 STUDY TREATMENT

All drugs in this trial are to be administered continuously. Although a cycle of treatment during this study is defined as 28 days, there are no scheduled interruptions in treatment. The division of treatment into 28-day cycles is solely for the purpose of guiding the timing of the safety, PK, pharmacodynamic, and efficacy evaluations that are performed during the study.

In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up).

NOTE: At the time any patient crosses over from the control arm to the combination arm in a randomized phase 2 study, the first cycle of combination treatment will be considered Cycle 1.

6.1 Details on Drug Administration

6.1.1 CPI-1205

CPI-1205 will be dosed TID or, as of Amendment 2, BID with cobicistat. Cohorts of CPI-1205 BID without cobicistat may also be evaluated. The CPI-1205 dose will not be adjusted for body weight or body surface area; all patients treated in the same cohort/at the same dose level will receive the same total milligram dose of CPI-1205 per day.

Patients will be given a dosing diary at the start of each treatment cycle. They will be asked to record in their dosing diaries information relevant to the administration of CPI-1205 (e.g., confirmation all daily doses were taken, reasons for missed doses).

For those on CPI-1205 PO TID, patients should be instructed to take each CPI-1205 dose at approximately the same time every day. The three daily doses should be separated by a minimum of 6 and a maximum of 8 hours. For those on CPI-1205 PO BID (with or without cobicistat), patients should be instructed to take each CPI-1205 dose at approximately the same time every day. The two daily doses should be separated by a minimum of 8 and a maximum of 12 hours. Each dose of CPI-1205 should be taken with a glass of water and consumed over as short a time as possible (e.g., all tablets within 5 minutes). Patients should be instructed to swallow tablets whole and to not chew them. No food or drink (other than water) should be taken for at least 1 hour before each dose and 1 hour after each dose. **NOTE:** Since fasting is required for 2 hours prior to abiraterone, when CPI-1205 and abiraterone are administered at the same time (e.g., the morning dose), no food or drink (other than water) should be taken for at least 2 hours before CPI-1205.

The morning (first) dose of CPI-1205 should be taken immediately prior to either enzalutamide or abiraterone/prednisone (if applicable), depending on the combination the patient is scheduled to receive. **NOTE:** See Section 6.1.2 for timing on cobicistat. Other prescribed medications may be taken with water up to 1 hour before and as soon as 1 hour after each dose of CPI-1205.

If a patient vomits up any portion of their dose of CPI-1205, they should not re-dose or attempt to make up the dose. Dosing would resume with next regularly scheduled dose.

If the patient forgets to take one of his scheduled doses, then he should take it within 3 hours after the missed dose. If more than 3 hours have passed, then that missed dose should be omitted, and the patient should resume treatment with the next scheduled dose.

6.1.2 Cobicistat

Patients on cobicistat will be asked to record in their dosing diaries information relevant to the administration of cobicistat (e.g., confirmation daily doses were taken, reasons for missed doses).

During Screening, patients will be provided with oral cobicistat to be started the evening prior to Cycle 1 day 1 (C1D1) of CPI-1205 (i.e., day 0), with one dose to be taken the evening of day 0 with food. Cobicistat will then be given BID starting on day 1 of CPI-1205, continuing throughout CPI-1205 dosing. **NOTE:** Site staff will call each patient within 24 hours prior to C1D1 to remind patient to take cobicistat as instructed.

Once CPI-1205 BID dosing begins, patients should be instructed to take each dose of cobicistat at least 1 hour after each CPI-1205 dose, with food.

NOTE: At the time any patient crosses over from the control arm to the combination arm in a randomized phase 2 study, the first cycle of combination treatment will be considered Cycle 1. For these patients, if cobicistat is part of the regimen, cobicistat must start the evening of day 0 with food. Cobicistat will then be given BID starting on day 1 of CPI-1205, continuing throughout CPI-1205 dosing as outlined above.

6.1.3 Enzalutamide

Patients will be given a dosing diary at the start of each treatment cycle. They will be asked to record in their dosing diaries information relevant to the administration of enzalutamide (e.g., confirmation daily doses were taken, reasons for missed doses).

Patients should be instructed to take their once daily 160mg dose of enzalutamide by ingesting four 40mg capsules orally at approximately the same time every day (in the morning) immediately after the first CPI-1205 dose (if applicable). All 4 capsules should be consumed over as short a time as possible (e.g., all capsules within 5 minutes).

[redacted]

6.1.4 Abiraterone/Prednisone

Patients will be given a dosing diary at the start of each treatment cycle. They will be asked to record in their dosing diaries information relevant to the administration of abiraterone (e.g., confirmation daily doses were taken, reasons for missed doses). Prednisone does not need to be documented on the diary.

Patients should be instructed to take their once daily 1000mg dose of abiraterone by ingesting four 250mg tablets orally at approximately the same time every day (in the morning) immediately after the first CPI-1205 dose (if applicable). All 4 tablets should be consumed over as short a time as possible (e.g., all within 5 minutes), and must be taken at least 1 hour before a meal or 2 hours after a meal. [redacted]

Patients will be instructed to take 5mg prednisone, BID (or with frequency of the prednisone at the discretion of the investigator). It is not required for the prednisone to be taken at the same time as the abiraterone or CPI-1205. If a prednisone dose is missed, it should be omitted and will not be made up.

[redacted]

6.2 Dose Modifications and Management of Toxicities

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Schedule of Events Tables (see Section 7). Toxicity will be assessed according to the NCI CTCAE, v4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity. During phase 1b (all cohorts) and in any phase 2 combination arm, the investigator

should carefully assess all treatment-associated toxicities and, whenever possible, determine if they can be attributed to CPI-1205 (with or without cobicistat), enzalutamide alone, abiraterone alone or to the respective combination regimen. **NOTE**: if the toxicity cannot be definitively attributed to enzalutamide or abiraterone, dose modification should be implemented at the discretion of the investigator (i.e., either CPI-1205 should be dose reduced or CPI-1205 as well as enzalutamide or abiraterone should be dose reduced). If the toxicity recurs then all protocol-mandated therapy should be discontinued.

One dose reduction from 800 mg PO TID to 600mg PO TID is allowed when CPI-1205 is given PO TID. One dose reduction from 800 mg PO BID to 600mg PO BID is allowed when CPI-1205 is given PO BID. The dose levels for CPI-1205 when given with cobicistat are 800mg PO BID, 600mg PO BID, 400mg PO BID and 200mg PO BID, with the chosen dose based on the starting dose. If a dose below 600mg PO TID or BID (of CPI-1205 without cobicistat) or 200mg PO BID (of CPI-1205 with cobicistat) is required, CPI-1205 must be permanently discontinued, and the patient followed-up per protocol. For enzalutamide, dose reductions in 40mg increments are allowed (e.g., from 160mg to 120mg, and from 120mg to 80mg). If a dose below 80mg is required, enzalutamide must be permanently discontinued. For abiraterone, dose reductions in 250mg increments are allowed (from 1000mg to 750mg, and from 750mg to 500mg). If a dose below 500mg is required, abiraterone must be permanently discontinued. Dose modifications for prednisone will be at the discretion of the investigator. Once the dose of a drug has been reduced, it cannot be increased at a later time.

NOTE: If CPI-1205, enzalutamide or abiraterone is held for toxicity, missed doses will not be made up. If CPI-1205 is held, cobicistat must also be held. If a dose reduction of CPI-1205 is required, the dose of cobicistat will remain the same (i.e., 150mg). There will be no dose modifications of cobicistat.

NOTE: During phase 1b (all cohorts) and in any phase 2 combination arm, if patients require that either enzalutamide or abiraterone be permanently discontinued, CPI-1205 (with or without cobicistat) may be continued at the discretion of the investigator. If CPI-1205 (with or without cobicistat) must be permanently discontinued, all protocol-mandated therapy should be discontinued, and the patient followed-up per protocol. If any of the drugs has to be held for >2 weeks for drug-related toxicity, all protocol-mandated therapy should be discontinued, and the patient followed-up per protocol.

NOTE: No dose modifications of cobicistat are recommended. However, as summarized in Section 1.4.1.2, cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function. This effect should be considered when interpreting changes in serum creatinine in patients on cobicistat. If serum creatinine rises above 0.4, investigators should consult with the Medical Monitor to determine if additional work-up is required, and/or dose adjustments in any other medications should be considered.

6.2.1 CPI-1205 (with or without Cobicistat) Dose Interruptions/Reductions

During a cycle of treatment CPI-1205 (with or without cobicistat) should continue to be administered as planned unless interruption of treatment is required as noted in Table 6-1.
NOTE: For patients enrolled in cohorts/study arms with cobicistat, if CPI-1205 is held, cobicistat must also be held. If a dose reduction of CPI-1205 is required, the dose of cobicistat will remain the same (i.e., 150mg). There will be no dose modifications of cobicistat.

Table 6-1 Dose Modifications and Monitoring for CPI-1205 Related Toxicities

Toxicity	Actions Required
Hematology	
Grade 4 neutropenia (ANC < 0.5 x 10^9/L)	• Hold CPI-1205 until resolves to ≤ Grade 1 and resume with dose reduced by one level • Repeat CBC at least weekly until resolves to ≤ Grade 1
≥ Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L and single oral temperature > 38.3°C or ≥ 38°C for >1 hour)	• Hold CPI-1205 until ANC resolves to ≤ Grade 1 and fever has resolved and resume with dose reduced by one level • Repeat CBC at least weekly until resolves to ≤ Grade 1
Grade 4 thrombocytopenia (platelets < 25 x 10^9/L) **OR** Grade 3 thrombocytopenia (platelets between 25-49 x 10^9/L) with bleeding or any requirement for platelet transfusion	• Hold CPI-1205 until resolves to ≤ Grade 2 and any bleeding has resolved and resume with dose reduced by one level • Repeat CBC at least weekly until resolves to ≤ Grade 2
Hepatic	
Grade 3 bilirubin (>3-10 x ULN) (except Gilbert's disease)	• Hold CPI-1205 until resolves to ≤ Grade 1 and resume with dose reduced by one level • Repeat serum bilirubin at least weekly until resolves to ≤ Grade 1. • Patients should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results.
Grade 3 ALT/AST (>5-20 x ULN) in patients who enroll with ≤ Grade 1 ALT/AST **OR** Tripling of ALT/AST in patients who enroll with Grade 2 ALT/AST	• Hold CPI-1205 until resolves to ≤ Grade 1 or baseline and resume with same dose if resolves in ≤ 7 days. If it lasts >7 days, resume with dose reduced by one level • Repeat serum transaminases at least weekly until resolved to ≤ Grade 1 or baseline.
> 2 x ULN bilirubin **AND** ≥ Grade 2 ALT/AST (>3 x ULN) in patients who enroll with ≤ Grade 1 ALT/AST **OR** > 2 x ULN bilirubin **AND** doubling of ALT/AST in patients who enroll with Grade 2 ALT/AST	• Permanently discontinue CPI-1205 in the absence of biliary obstruction or other causes responsible for the concurrent elevation
Grade 4 ALT/AST **OR** Grade 4 bilirubin	• Permanently discontinue CPI-1205

Toxicity	Actions Required
Metabolic	
Grade 3 electrolyte disturbance	• Hold CPI-1205 until resolves to ≤ Grade 1 and resume with same dose if resolves in ≤ 72 hours or with dose reduced by one level if resolution takes >72 hours.
Grade 4 electrolyte disturbance	• Hold CPI-1205 until resolves to ≤ Grade 1 and resume with same dose if resolves in ≤ 72 hours; permanently discontinue if resolution takes >72 hours.
Gastrointestinal (see Supportive Care Section 6.3)	
Grade 3 vomiting, diarrhea or Grade 3 nausea	• Hold CPI-1205 until resolves to ≤ Grade 1 and resume with same dose if resolves in ≤ 72 hours with supportive care. If it lasts >72 hours despite optimal supportive care, resume with dose reduced by one level. • Patients must be contacted by the investigator or study nurse daily until it is clear that the problem has resolved or requires additional support (e.g., hospitalization).
Grade 4 vomiting or diarrhea	• Hold CPI-1205 until resolves to ≤ Grade 1 and resume with same dose if resolves in ≤ 72 hours with supportive care. If it lasts >72 hours despite optimal supportive care, permanently discontinue. • Patients must be contacted by the investigator or study nurse daily until it is clear that the problem has resolved or requires additional support (e.g., hospitalization).
Other Non-specified	
Grade 2 or Grade 3 that, in the opinion of the investigator, require dose reduction	• Hold CPI-1205 until resolves to ≤ Grade 1 and resume with dose reduced by one level • Evaluate at least once weekly following the initial identification of the toxicity until its resolution or stabilization.
Grade 4[a]	• Permanently discontinue CPI-1205
Treatment delay >2 weeks	• Permanently discontinue CPI-1205
[a]Other than laboratory abnormalities that investigator deems clinically insignificant and that last ≤48 hours	

6.2.2 Enzalutamide Dose Interruptions/Reductions

Table 6-2 Dose Modifications and Monitoring for Enzalutamide Related Toxicities

Toxicity	Grade	Actions required
Seizure	Any	• Permanently discontinue enzalutamide • Manage seizure per investigator discretion
Posterior reversible encephalopathy Syndrome (PRES)	Any	• Permanently discontinue enzalutamide • Manage per investigator discretion
Allergic reaction/ hypersensitivity	Any symptoms (e.g., edema of face, lips, tounge, throat)	• Temporarily discontinue enzalutamide • Manage per investigator discretion **NOTE:** If reaction is serious, enzalutamide should be permanently discontinued
Ischemic heart disease/events	3 or 4	• Permanently discontinue enzalutamide • Manage per investigator discretion
Non-specified	3 despite optimal medical management	• Hold enzalutamide until ≤ Grade 2 • Manage per investigator discretion • Resume enzalutamide reduced by one dose level[a].
	4	• Permanently discontinue enzalutamide[b]

Toxicity	Grade	Actions required
[a]Dose reductions in 40mg increments are allowed (e.g., from 160mg to 120mg, and from 120mg to 80mg). If a dose below 80mg is required, enzalutamide must be discontinued. [b]Other than laboratory abnormalities that investigator deems clinically insignificant and that last ≤48 hours		

6.2.3 Enzalutamide Dose Increases

When enzalutamide is combined with a strong CYP3A4 inducer, the US prescribing information for enzalutamide (see www.xtandi.com) recommends increasing the dose from 160mg PO QD to 240mg PO QD. Based on this, in combination cohorts/study arms only, the dose of enzalutamide may be increased after Cycle 2 based on the specific patient's PK results*, and only after consultation with the Medical Monitor. **NOTE:** The dose of enzalutamide may NOT be increased in any patient who requires a dose reduction of enzalutamide for toxicity. Any increase in dose must start at the beginning of a cycle (e.g., day 1 of Cycle 3). After any increase, a blood sample for PK must be taken on day 1 of the following cycle (e.g., day 1 of Cycle 4). **NOTE:** if any dose reductions for enzalutamide are required after any dose increase, the dose of enzalutamide may **NOT** be increased again. Any dose decrease required after an increase should be made in 40mg increments. *The enzalutamide dose cannot be increased in patients enrolled in a HPEC who do not consent PK.

6.2.4 Abiraterone Dose Interruptions/Reductions

Table 6-3 Dose Modifications and Monitoring for Abiraterone Related Toxicities

Toxicity	Actions Required
Hypokalemia (see Supportive Care Section 6.3)	
≤ Grade 2 (serum potassium < 3.5 mmol/L or less than institutional limits of normal (LLN) but ≥ 3.0 mmol/L) with or without symptoms	• Maintain abiraterone dose • Initiate potassium supplementation and titrate dose of supplementation to maintain serum potassium within institutional normal limits (WNL)
Grade 3 (< 3.0 to 2.5 mmol/L)	• Hold abiraterone until resolves to ≤ Grade 2 and resume with dose reduced by one level • Initiate IV potassium and cardiac monitoring
Grade 4 (<2.5 mmol/L)	• Hold abiraterone until resolves to ≤ Grade 1 and resume with dose reduced by one level if resolves in ≤ 72 hours; permanently discontinue if resolution takes >72 hours. • Initiate IV potassium and cardiac monitoring
Hypertension	
Grade 1-2	• Maintain abiraterone dose • Manage hypertension per investigator discretion
Grade 3-4	• Hold abiraterone until resolves to ≤ Grade 1 and resume at full dose • Manage hypertension per investigator discretion • If toxicity recurs, hold abiraterone until resolves to ≤ Grade 1 and resume abiraterone reduced by one dose level[a].
Edema/Fluid Retention	
Grade 1-2	• Maintain abiraterone dose • Manage per investigator discretion
Grade 3 generalized edema, or Grade 3 pulmonary edema (i.e., requires oxygen)	• Hold abiraterone until resolves to ≤ Grade 1 and resume at full dose • Manage per investigator discretion • If toxicity recurs, hold abiraterone until resolves to ≤ Grade 1 and resume abiraterone reduced by one dose level[a].
Grade 4 generalized edema or Grade 4 pulmonary edema (i.e., requires oxygen)	• Permanently discontinue
Hepatic	
Grade 3 bilirubin (>3-10 x ULN)	• Hold abiraterone until resolves to ≤ Grade 1 or baseline and resume with dose reduced by one level [a]. • Repeat serum bilirubin at least twice a week until resolution to Grade 2, and then at least once a week until resolved to ≤ Grade 1.
Grade 3 ALT/AST (>5-20 x ULN) in patients who enroll with ≤ Grade 1 ALT/AST **OR** Tripling of AST/ALT in patients who enroll with Grade 2 ALT/AST	• Hold abiraterone until resolves to ≤ Grade 1 or baseline and resume abiraterone reduced by one dose level. • Repeat serum transaminases at least twice a week until resolution to Grade 2, and then at least once a week until resolved to ≤ Grade 1 or baseline. • If toxicity recurs, hold abiraterone until resolves to ≤ Grade 1 or baseline or baseline and resume abiraterone reduced by one dose level[a].
> 2 x ULN bilirubin **AND** ≥ Grade 2 ALT/AST (>3 x ULN) in patients who enroll with ≤ Grade 1 ALT/AST	• Permanently discontinue abiraterone in the absence of biliary obstruction or other causes responsible for the concurrent elevation

Toxicity	Actions Required
OR > 2 x ULN bilirubin **AND** doubling of ALT/AST in patients who enroll with Grade 2 ALT/AST	
Grade 4 ALT/AST **OR** Grade 4 bilirubin	• Permanently discontinue abiraterone
Other Non-specified	
Grade 3 including headache, nausea, vomiting, diarrhea, or any other toxicity judged related to abiraterone	• Hold abiraterone until resolves to ≤ Grade 1 or baseline and resume at full dose. • If toxicity recurs, hold abiraterone until resolves to ≤ Grade 1 and resume abiraterone reduced by one dose level.[a]
Grade 4[b]	• Permanently discontinue abiraterone
Treatment delay >2 weeks	• Permanently discontinue abiraterone
[a]Dose reductions in 250mg increments are allowed (e.g., from 1000mg to 750mg, and from 750mg to 500mg). If a dose below 500mg is required, abiraterone must be discontinued. [b]Other than laboratory abnormalities that investigator deems clinically insignificant and that last ≤48 hours	

6.2.5 Abiraterone Dose Increases

When abiraterone is combined with a strong CYP3A4 inducer, the US prescribing information for abiraterone (see www.zytiga.com) recommends increasing the dose from 1000mg PO QD to 1000mg PO BID. Based on this, in combination cohorts/study arms only, the dose of abiraterone may be increased after Cycle 2 based on the specific patient's PK results*, and only after consultation with the Medical Monitor. **NOTE:** The dose of abiraterone may NOT be increased in any patient who requires a dose reduction of abiraterone for toxicity. Any increase in dose must start at the beginning of a cycle (e.g., day 1 of Cycle 3). After any increase, a blood sample for PK must be taken on day 1 of the following cycle (e.g., day 1 of Cycle 4). **NOTE:** If CPI-1205/cobicistat is discontinued but the patient continues on abiraterone off-protocol, the dose frequency of abiraterone should return to once daily. **NOTE:** if any dose reductions for abiraterone are required after any dose increase, the dose of abiraterone may **NOT** be increased again. Any dose decrease required after an increase should be made in 250mg increments. *The abiraterone dose cannot be increased in patients enrolled in a HPEC who do not consent to PK.

6.2.6 Prednisone Dose Interruptions/Reductions

See Section 9.5.1 for a summary of AEs associated with glucocorticoids. Management of any of these AEs will be at the discretion of the investigator.

Of note, a detailed analysis was undertaken of 2,267 patients enrolled in the two randomized phase 3 trials of abiraterone. Researchers concluded that side effects attributable to prednisone were limited, and that long term treatment with this low dose was safe and tolerable. The two most frequent AEs of any grade in the abiraterone plus prednisone group associated with corticosteroids were hyperglycemia (7.8%) and weight gain (3.9%) [75].

Low dose prednisone is approved in combination with abiraterone to help mitigate the AEs associated with mineralocorticoid excess, i.e., hypokalemia, hypertension and edema as well as

fatigue from the reduction in cortisol (see Section 1.1.1.1). Therefore, any adjustments in the dose or schedule of prednisone may lead to an increase in abiraterone related AEs. In addition, adrenocortical insufficiency may occur following any interruption in prednisone dosing, or with concurrent infection or stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone. Therefore, if clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency.

6.3 Concomitant Medications

See the appendices for a list of drugs, fruits and juices that are prohibited (Appendix 4), or to be used with caution (Appendix 5) while on CPI-1205, cobicistat, enzalutamide or abiraterone. In addition, patients are prohibited from taking any other agents for the treatment of prostate cancer including first generation AR antagonists, 5 alpha reductase inhibitors, ketoconazole, estrogens (including DES), progesterones, chemotherapy, biologic therapy, radionuclide therapyor immunotherapy. In addition, patients may not take herbal products that may decrease PSA levels, or systemic steroids greater than the equivalent of 10 mg of prednisone/prednisolone per day.

NOTE: Patients who have not undergone surgical castration must continue their medical castration, i.e., GnRH analog or antagonist, for the duration of study treatment.

[redacted]

6.3.2 Cobicistat

6.3.2.1 CYP3A Inhibitors and Inducers

Cobicistat is metabolized by CYP3A, and to a minor extent, by CYP2D6. **Therefore, patients who are receiving cobicistat are prohibited from concomitantly taking drugs or other substances known to be strong inhibitors of CYP3A.** Likewise, patients should be instructed to avoid certain fruits and juices as well due to their potential to interact with CYP3A. It is further recommended that moderate CYP3A inhibitors should be used with caution (i.e., consider additional monitoring) and avoided if reasonable alternatives are available.

Concomitant treatment with drugs or substances known to be strong inducers of CYP3A activity are prohibited for patients receiving cobicistat other than enzalutamide (if applicable). Drugs or substances that are moderate or weak inducers of CYP3A should be used with caution (i.e., consider additional monitoring) and avoided if reasonable alternatives are available.

6.3.2.2 CYP3A4 and CYP2D6 Substrates with Narrow Therapeutic Index

Cobicistat is a CYP3A and CYP2D6 inhibitor. **Therefore, CYP3A4 and CYP2D6 substrates with a narrow therapeutic index are also prohibited for patients receiving cobicistat**.

6.3.2.3 Other CYP3A Substrates

CYP3A substrates that do not have a narrow therapeutic index may still require additional monitoring and/or dose adjustments when used concomitantly with cobicistat due to increases in plasma concentrations. When possible, consider alternative agents. If use of an alternative agent is not appropriate, careful dose titration of the CYP3A substrate to the desired effect should be performed, including using the lowest feasible initial or maintenance dose, and monitoring for response and toxicity.

Concomitant use of cobicistat with quetiapine requires a dramatic dose reduction of quetiapine. **Therefore, concomitant administration of quetiapine is prohibited for patients receiving cobicistat.**

Concomitant use of phosphodiesterase-5 (PDE-5) inhibitors sildenafil or tadalafil for the treatment of pulmonary arterial hypertension is prohibited for patients receiving cobicistat. When used for the treatment of erectile dysfunction, sildenafil may be used at a single dose not exceeding 25 mg in 48 hours, tadalafil at a single dose not exceeding 10 mg in 72 hours,

or vardenafil at a single dose not exceeding 2.5 mg in 72 hours. Patients should be monitored for PDE-5 inhibitor associated adverse events.

6.3.2.4 Substrates of P-gp, BCRP, OATP1B1 and OATP1B3

The transporters that cobicistat inhibits include p-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. The plasma concentration of drugs that are substrates of P-gp, BCRP, OATP1B1, or OATP1B3 may be increased if those drugs are coadministered with cobicistat. It is recommended that substrates of P-gp, BCRP, OATP1B1 or OATP1B3 be used with caution (i.e., consider additional monitoring) and avoided if reasonable alternatives are available.

Patients on rosuvastatin, atorvastatin, pitavastatin or pravastatin should be closely monitored for statin-related side effects (e.g., myopathy) as levels of these agents may increase in patients on cobicistat.

NOTE: concomitant use of PgP inhibitors in patient with moderate to severe renal impairment (<50 mL/min) may produce increased exposure to the anticoagulant dabigatran etexilate. **Therefore, dabigatran etelixate is prohibited in patients on cobicistat with moderate or several renal impairment.**

6.3.2.5 Corticosteroids (Systemic, Inhaled, Nasal, Ophthalmic)

Coadministration with corticosteroids whose exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone (whose PK and/or pharmacodynamics are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.

6.3.2.6 Miscellaneous

The use of colchicine is contraindicated in patients on cobicistat who have renal and/or hepatic impairment. **The use of colchicine is prohibited in this trial in patients receiving cobicistat.**

One moderate to weak CYP3A inducer that is prohibited in patients receiving cobicistat is bosentan.

The effects of cobicistat on the PK of warfarin are unknown. Monitor the international normalized ratio (INR) when coadministering with warfarin.

Clinical monitoring is recommended upon co-administration of cobicistat with antiarrhythmics.

The effects of cobicistat on the PK of serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants are unknown. When co-administering an agent from this class of drugs with cobicistat, careful dose titration of the anti-depressant to the desired effect, including using the lowest feasible initial or maintenance dose, and monitoring for antidepressant response are recommended.

Patients on fluvastatin should be closely monitored for statin-related side effects (e.g., myopathy) as levels of these agents may increase in patients on cobicistat.

6.3.3 Enzalutamide

6.3.3.1 CYP2C8 and CYP3A4 Inducers

In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. **The concomitant use of strong CYP2C8 inhibitors and CYP3A4 inducers with enzalutamide are prohibited.** The major circulating metabolites of enzalutamide inhibit multiple CYP450 enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5.

6.3.3.2 CYP3A4, CYP2C9 and CYP2C19 Substrates

Enzalutamide is a strong CYP3A4 inducer and moderate inducer of CYP2C9 and CYP2C19. **Concomitant use of enzalutamide with narrow therapeutic index drugs that are substrates of these enzymes are prohibited.**

6.3.4 Abiraterone

6.3.4.1 CYP3A4 Inducers

In vitro, human CYP3A4 is responsible for the metabolism of abiraterone. **The concomitant use of strong CYP3A4 inducers with abiraterone is prohibited.**

6.3.4.2 CYP2D6 Substrates

Abiraterone is an inhibitor of CYP2D6. **Concomitant use of abiraterone with narrow therapeutic index drugs that are substrates of CYP2D6 is prohibited.**

6.3.4.3 CYP2C8 Substrates

Abiraterone is an inhibitor of CYP2C8. Drugs or substances that are substrates of CYP2C8 with a narrow therapeutic index should be used with caution (i.e., consider additional monitoring) and avoided if reasonable alternatives are available.

6.3.5 Permitted Supportive Care

Unless otherwise prohibited (See Section 6.3), supportive therapy for optimal medical care may be administered per institutional standard of care at the study centers. Efforts should be made to keep all other concurrent medications at stable doses during the study and to refrain from starting any new medications, unless clinically indicated. Patients may receive supportive care (e.g., transfusion with packed red blood cells [PRBCs]) as per local institutional guidelines.

Palliative radiation therapy to bone and initiation of bisphosphonates, denosumab or other approved bone targeting agents are allowed and should not result in discontinuation of CPI-1205 drug therapy.

6.3.5.1 Management of Nausea and/or Vomiting

Prophylactic anti-emetic therapy will not be used in this study. If management of nausea/vomiting is needed, 5-hydroxytryptamine (5-HT3) receptor antagonists and benzodiazepines (e.g., lorazepam) should be tried first. In prior studies with CPI-1205, most patients had good symptomatic improvement using 8 mg ondansentron TID as needed.

[redacted]

6.3.5.2 Management of Diarrhea

Loperamide will not be used prophylactically. However, patients will be instructed to take loperamide, 4mg, at the occurrence of the first loose stool and then 2mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, patients may take 4mg of loperamide every 4 hours. Fluid intake should be maintained to avoid dehydration.

6.3.5.3 Hematopoietic Growth Factors

Granulocytic and granulocytic/monocytic colony stimulating factors (e.g., G-CSF [filgrastim or equivalent], GM-CSF) will not be used in this trial in a manner that would support dose escalation of CPI-1205. However, filgrastim or equivalent may be used to support patients who have developed Grade 4 neutropenia or ≥ Grade 3 neutropenia with fever and/or infection. Use of peg-filgrastim is not permitted.

The use of erythropoietin is permitted according to the American Society of Clinical Oncology (or other institutional) Guidelines.

6.3.5.4 Electrolytes

Monitor electrolytes and provide electrolyte supplementation if warranted.

6.4 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in Section 6.2, a patient will also be discontinued from protocol therapy and followed up per protocol under the following circumstances:

- Radiographic disease progression (as determined by the investigator) or unequivocal clinical progression (see Section 10.4) or SRE (see Section 10.6) **AND** planned initiation of other systemic treatment for prostate cancer; **NOTE:** When this happens to patients in the control arm of any randomized phase 2 trial conducted, patients will have the option to cross over to the combination arm provided they are eligible (see Section 5.5.1). Treatment will continue in 28-day cycles until unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE **AND** planned initiation of other systemic treatment for prostate cancer or until unacceptable toxicity.

- The treating physician thinks a change of therapy would be in the best interest of the patient

- The patient requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons

NOTE: PSA rise without evidence of radiographic progression, unequivocal clinical progression or without a SRE will not be used as a criterion to start a new systemic anti-neoplastic therapy throughout the study.

7 SCHEDULE OF EVENTS AND DETAILS ON STUDY PROCEDURES

7.1 Schedule of Events Tables

The Schedule of Events is presented in Table 7-1 for phase 1b dose escalation and in Table 7-2 for the phase 1b HPEC(s). The Schedule of Events for phase 2 is presented in Table 7-3. Table 7-4 is the Schedule of Events for patients who cross over to the combination arm from the control arm of a randomized phase 2 (and for patients in phase 1b Dose Level 1A [CPI-1205 PO TID without cobicistat] who switch to CPI-1205 PO BID with cobicistat). **NOTE:** At the time any patient crosses over from the control arm to the combination arm, the first cycle of combination treatment will be considered Cycle 1.

The Screening period includes the 28 days before day 1 of treatment. Screening assessments should be performed within 28 days prior to C1D1 unless otherwise noted in the footnotes. **NOTE:** in order to minimize the volume of blood collected during a single visit, all blood samples do not have to be collected on the same day during Screening.

There is no window for visits during Cycles 1 and 2, however, clinical laboratory parameters (see Section 7.3.5.7) may be drawn within 48 hours prior to day of visit. Starting in Cycle 3, a window of ± 3 days will be applied to all clinic visits. When applicable, specific windows for assessments (e.g., 6 hours [±1 hr]) are provided in the footnotes.

Table 7-1 Schedule of Events Phase 1b Dose Escalation: CPI-1205 with or without Cobicistat in Combination with Abiraterone or Enzalutamide in 28-Day Cycles

Assessment	Screening[a]	Cycle 1[a]						Cycle 2[a]				Cycle 3[a]		Cycle 4[a]		Cycles 5+[a]	End of Treatment Visit[b]	Safety Follow-up Visit[c]	Follow-up for Patients Without Disease Progression[d]
	Days 28 to -1	D1	D2	D8	D15	D16	D22	D1	D2	D15	D16	D1	D15	D1	D2	D1			
Informed consent	X																		
Study entry criteria	X																		
Demographics	X																		
Medical history	X																		
Signs & symptoms/ Physical examination	X[e]	X[e,f]						X[f]				X[f]		X[f]		X[f]	X[f]	X[e]	
ECOG performance status	X	X						X				X		X		X	X	X	
Vital signs	X	X[g]						X				X		X		X			
ECG	X	X[g]																X	
Coagulation[h]	X							X											
Hematology[h]	X	X[i]		X	X		X	X		X		X	X	X		X	X	X	
Clinical chemistry[h]	X	X[i]		X	X		X	X		X		X	X	X		X	X	X	
Serum lipids and creatine phosphokinase (CPK)	X	X[i]						X				X		X		X	X	X	
Thyroid function tests[h]	X											X				X[h]			
Other Endocrinology[h]	X							X						X					
PSA[i]	X	X[i]						X				X		X		X	X		X
CTC enumeration	X							X[j]				X[j]		X[j]		X[j]	X[j]		X
CT/MRI	X							See footnote k									X		X
Bone scan	X							See footnote k									X		X
Blood sample for PK		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[m]	X[m]			X[l]	X[l]				
[redacted]																			

[redacted]

CPI-1205 administration		TID without cobicistat (Cohorts 1A or [-]1A) or BID with cobicistat (Cohorts 1B, 2B and [-]1B) or BID without cobcistat (if applicable)																	
Abiraterone **OR** enzalutamide administration[o]		See footnote o																	
Cobicistat administration		BID Dosing in Cohorts 1B, 2B and (-)1B only; see footnote p																	
Patient diary								X				X		X		X	X		

[redacted]

Adverse events	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	X	X	X	X	X	

a. Screening assessments should be performed within 28 days prior to C1D1 unless otherwise noted. **NOTE:** in order to minimize the volume of blood collected during a single visit, all blood samples do not have to be collected on the same day during Screening. There is no window for visits during Cycles 1 and 2, however, clinical laboratory parameters (see Section 7.3.5.7) may be drawn within 48 hours prior to day of visit. Starting in Cycle 3, a window of ± 3 days will be applied to all clinic visits.

b. The End of Treatment Visit should occur ≤ 7 days after the last dose of CPI-1205. If the patient had all the end of treatment assessments completed ≤ 7 days prior to the last dose of CPI-1205, these assessments do not need to be repeated at the End of Treatment Visit. **NOTE:** CT/MRI and bone scan do not need to be repeated if completed ≤ 28 days prior to the last dose of CPI-1205

c. The Safety Follow-up Visit should occur 30 days (± 10 days) after the last dose of CPI-1205.

d. Patients who discontinue study treatment for reasons other than radiographic progression will continue to have their disease evaluated by PSA, CT/MRI,bone scan and CTC enumeration (if study treatment is discontinued prior to the last scheduled CTC collection). PSA and CTCs will be measured and imaging will be performed at the End of Treatment Visit; CTC enumeration and subsequent imaging should follow the same schedule as if patient had continued on treatment as outlined in footnotes j and k, respectively, until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. After the End of Treatment Visit, PSA should be measured each time imaging is performed.

e. A complete physical examination (including height [Screening only] and weight) and a signs and symptoms assessment will be performed during Screening and at the Safety Follow-up Visit. Physical exam/signs and symptoms assessment do not need to be repeated on C1D1 if the Screening evaluations are conducted ≤ 3 days prior to C1D1. In this case, the Screening evaluations will be considered baseline.

f. Assessment of signs and symptoms and an abbreviated physical examination (including weight) will be performed on D1 of each cycle and at the End of Treatment Visit. For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease (e.g., chest pain or discomfort at rest or with activity or shortness of breath) and hypersensitivity reactions.

g. Obtained prior to dosing and at 3 h (± 30 min) after dosing on C1D1. Subsequent ECGs will only be performed during treatment if clinically indicated.

h. Hematology: complete blood count (CBC) with differential (includes hemoglobin, total white blood cell (WBC) count, differential WBC count, and platelet count).
Serum Chemistries: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, albumin, AST, ALT, lactate dehydrogenase (LDH), uric acid, calcium, magnesium, phosphate, serum glucose.
Coagulation Parameters: prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT)
Thyroid Function Tests: Thyroid stimulating hormone (TSH) and T4; to be collected at Screening, C3D1 and every other cycle thereafter

Other Endocrinology: sex hormone-binding globulin (SHBG), androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate, dihydrotestosterone (DHT), estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin and total testosterone. **NOTE:** serum testosterone must be <50 ng/dL at Screening.

i. **NOTE:** C1D1 laboratory assessments must be reviewed and results must fulfill applicable inclusion criteria prior to initiation of dosing. If Screening assessment (other than PSA) was performed ≤ 3 days prior to C1D1, it does not need to be repeated C1D1. If Screening assessment for PSA was performed ≤ 7 days prior to C1D1, it does not need to be repeated C1D1. **NOTE:** PSA50 is defined as a ≥50% reduction in PSA from baseline. The reduction must be confirmed by a second PSA value 4 or more weeks later (see Section 10.1.2).
j. During treatment, after C4D1, repeat CTC enumeration on C7D1 only. A + 7-day window applies to all CTC collections during treatment. **NOTE:** Any CTC 30% response and any conversion from unfavorable to favorable CTC status must be confirmed by an additional CTC enumeration at least 4 weeks later (see Section 10.5).
k. CT/MRI and bone scan should be done during Screening, every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) until radiographic progression (as determined by investigator). See Section 7.3.7.3 for additional details on the imaging procedures. **NOTE:** Changes in tumor measurements indicative of a response must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met (see Section 10.2.3). **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule.
l. On C1D1, C1D15, C2D1 and C4D1, a PK blood sample will be collected prior to the first dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients receiving CPI-1205 TID. On C1D8 and C1D22 a PK blood sample will be collected prior to the first dose of CPI-1205. **NOTE:** The enzalutamide dose and/or abiraterone dose may be increased after Cycle 2 based on the specific patient's PK results and only after consultation with the Medical Monitor. If a dose increase is implemented, an additional blood sample for PK is required. See Sections 6.2.3 and 6.2.5.
m. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide only, on C2D15 a PK blood sample will be collected prior to the morning dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients receiving CPI-1205 TID. AEs/concomitant medications will only be assessed on C2D16 for patients receiving enzalutamide. There will be no visit on C2D16 for patients receiving CPI-1205 + abiraterone/prednisone.
n. [redacted]
o. Patients enrolled in the CPI-1205 (with or without cobicistat) + enzalutamide cohorts will receive enzalutamide orally, once daily. Patients enrolled in the CPI-1205 (with or without cobicistat) + abiraterone/prednisone cohorts will receive abiraterone orally, once daily, plus prednisone orally BID (or with frequency of prednisone administration at the discretion of the investigator).
p. During Screening, patients enrolled in cohorts 1B, 2B and (-)1B will be provided with oral cobicistat to be started the evening of day 0 given with food. Cobicistat will then be given BID starting on day 1 of CPI-1205, continuing throughout CPI-1205 dosing. Patients will be instructed on when and how to take this medication by the study staff. **NOTE:** Site staff will call each patient within 24 hours prior to C1D1 to remind patient to take cobicistat as instructed.

[redacted]

Table 7-2 Schedule of Events Phase 1b HPEC(s): CPI-1205 with or without Cobicistat in Combination with Abiraterone or Enzalutamide in 28-Day Cycles

Assessment	Screening	Cycle 1[a]		Cycle 2[a]			Cycle 3[a]	Cycles 4+[a]	End of Treatment Visit[b]	Safety Follow-up Visit[c]	Follow-up for Patients Without Disease Progression[d]	Long Term Survival Follow-up[r]
	Days -28 to -1	D1	D15	D1	D2	D15/ D16	D1	D1				
Informed consent	X											
Study entry criteria	X											
Demographics	X											
Medical history	X											
Signs & symptoms/ Physical examination	X[e]	X[e,f]		X[f]			X[f]	X[f]	X[f]	X[e]		
ECOG performance status	X	X		X			X	X	X	X		
Vital signs	X	X[g]		X			X	X				
ECG	X	X[g]								X		
Coagulation[h]	X			X								
Hematology[h]	X	X[i]	X	X			X	X	X	X		
Clinical chemistry[h]	X	X[i]	X	X			X	X	X	X		
Serum lipids and creatine phosphokinase (CPK)	X	X[i]		X			X	X	X	X		
Thyroid Function Tests[h]	X						X	X[h]				
Other Endocrinology[h]	X			X				Cycle 4 only				
PSA[i]	X	X[i]		X			X	X	X		X	
CTC enumeration	X			X[j]			X[j]	Cycles 4 and 7 only[j]	X[j]		X	
CT/MRI[k]	X			See footnote k					X		X	
Bone Scan[k]	X			See footnote k					X		X	
Blood sample for PK		X[l]	X[l]	X[l]	X[l]	X[m]	X[l]					
[redacted]												

[redacted]

Cobicistat administration (if applicable)	See footnote o											
CPI-1205 administration		See footnote p										
Enzalutamide **OR** abiraterone administration		See footnote q										
Patient diary				X			X	X	X			
[redacted]												
Adverse events	X	X	X	X	X[l]	X[m]	X	X	X	X		
Concomitant medications	X	X	X	X	X[l]	X[m]	X	X	X	X		
Survival status												X[r]

a. Screening assessments should be performed within 28 days prior to C1D1 unless otherwise noted. **NOTE:** in order to minimize the volume of blood collected during a single visit, all blood samples do not have to be collected on the same day during Screening. There is no window for visits during Cycles 1 and 2, however, clinical laboratory parameters (see Section 7.3.5.7) may be drawn within 48 hours prior to day of visit. Starting in Cycle 3, a window of ± 3 days will be applied to all clinic visits.
b. The End of Treatment Visit should occur ≤ 7 days after the last dose of CPI-1205. If the patient had all the end of treatment assessments completed ≤ 7 days prior to the last dose of CPI-1205, these assessments do not need to be repeated at the End of Treatment Visit. **NOTE:** CT/MRI and bone scan do not need to be repeated if completed ≤ 28 days prior to the last dose of CPI-1205.
c. The Safety Follow-up Visit should occur 30 days (± 10 days) after the last dose of CPI-1205.
d. Patients who discontinue study treatment for reasons other than radiographic progression will continue to have their disease evaluated by PSA, CT/MRI, bone scan and CTC enumeration (if study treatment is discontinued prior to the last scheduled CTC collection). PSA and CTCs will be measured and imaging will be performed at the End of Treatment Visit; CTC enumeration and subsequent imaging should follow the same schedule as if patient had continued on treatment as outlined in footnotes j and k, respectively, until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. After the End of Treatment Visit, PSA should be measured each time imaging is performed.
e. A complete physical examination (including height [Screening only] and weight) and a signs and symptoms assessment will be performed during Screening and at the Safety Follow-up Visit. Physical exam/signs and symptoms assessment do not need to be repeated on C1D1 if the Screening evaluations are conducted ≤ 3 days prior to C1D1. In this case, the Screening evaluations will be considered baseline.
f. Assessment of signs and symptoms and an abbreviated physical examination (including weight) will be performed on D1 of each cycle and at the End of Treatment Visit. For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease (e.g., chest pain or discomfort at rest or with activity or shortness of breath) and hypersensitivity reactions.

g. Obtained prior to dosing and at 3 h (± 30 min) after dosing on C1D1. Subsequent ECGs will only be performed during treatment if clinically indicated.
h. Hematology: complete blood count (CBC) with differential (includes hemoglobin, total white blood cell (WBC) count, differential WBC count, and platelet count).
Serum Chemistries: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, albumin, AST, ALT, lactate dehydrogenase (LDH), uric acid, calcium, magnesium, phosphate, serum glucose.
Coagulation Parameters: prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT)
Thyroid Function Tests: Thyroid stimulating hormone (TSH) and T4; to be collected at Screening, C3D1 and every other cycle thereafter
Other Endocrinology: sex hormone-binding globulin (SHBG), androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate, dihydrotestosterone (DHT), estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and total testosterone. **NOTE:** serum testosterone must be <50 ng/dL at Screening.
i. **NOTE:** C1D1 laboratory assessments must be reviewed and results must fulfill applicable inclusion criteria prior to initiation of dosing. If Screening assessment (other than PSA) was performed ≤ 3 days prior to C1D1, it does not need to be repeated C1D1. If Screening assessment for PSA was performed ≤ 7 days prior to C1D1, it does not need to be repeated C1D1. **NOTE:** PSA50 is defined as a ≥50% reduction in PSA from baseline. The reduction must be confirmed by a second PSA value 4 or more weeks later (see Section 10.1.2).
j. During treatment, after C4D1, repeat CTC enumeration on C7D1 only. A + 7 day window applies to all CTC collections during treatment. **NOTE:** Any CTC 30% response and any conversion from unfavorable to favorable CTC status must be confirmed by an additional CTC enumeration at least 4 weeks later (see Section 10.5).
k. CT/MRI and bone scan should be done during Screening every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) thereafter until radiographic progression (as determined by the investigator). See Section 7.3.7.3 for additional details on the imaging procedures. **NOTE:** Changes in tumor measurements indicative of a response must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met (see Section 10.2.3). **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule.
l. PK sampling is required in at least 10 patients in any HPEC. PK blood samples will be collected at the following timepoints: C1D1, C1D15 and C3D1 prior to the first dose of CPI-1205; C2D1 prior to the first dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected on C2D1 in patients receiving CPI-1205 TID. AEs/concomitant medications will only be assessed on C2D2 in patients who consent to PK sampling. There will be no visit on C2D2 for patients who do not consent to PK sampling. **NOTE:** the enzalutamide and/or abiraterone dose may be increased after Cycle 2 based on the specific patient's PK results and only after consultation with the Medical Monitor. If a dose increase is implemented, an additional blood sample for PK is required. See Sections 6.2.3 and 6.2.5.
m. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide only (and who consent to PK), on C2D15 a PK blood sample will be collected prior to the morning dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients receiving CPI-1205 TID. AEs/concomitant medications will only be assessed on C2D15 and C2D16 for patients receiving enzalutamide who consent to PK. AEs/concomitant medications will not be assessed on C2D15 or C2D16 in patients receiving enzalutamode who do not consent to PK or in those receiving CPI-1205 (with or without cobicistat) + abiraterone/prednisone as there will be no visit on C2D15 or C2D16 for these patients.
n. [redacted]
o. During Screening, if a patient is to receive CPI-1205/cobicistat, the patient will be provided with oral cobicistat to be started the evening of day 0 and taken with food. Cobicistat will then be given BID starting on day 1 of CPI-1205, continuing throughout CPI-1205 dosing. Patients will be instructed on when and how to take this medication by the study staff. **NOTE:** Site staff will call each patient within 24 hours prior to C1D1 to remind patient to take cobicistat as instructed.
p. CPI-1205 will be administered PO TID without cobicistat or BID with or without cobicistat depending on the regimen chosen for the HPEC.
q. Enzalutamide will be given orally, once daily to patients enrolled in any CPI-1205 + enzalutamide HPEC. Abiraterone will be given orally, once daily, plus prednisone orally BID (or with frequency of prednisone administration at the discretion of the investigator) in any CPI-1205 + abiraterone/prednisone HPEC.

r. Long-term follow-up will begin after the Safety Follow-up Visit. All patients will be followed every 3 months until death or the study is closed to collect survival status. Contact can be conducted via telephone.

[redacted]

Table 7-3 Schedule of Events Phase 2: Randomized or Single-Arm With or Without Cobicistat

Assessment	Screening	Cycle 1[a]		Cycle 2[a]			Cycle 3[a]	Cycles 4+[a]	End of Treatment Visit[b]	Safety Follow-up Visit[c]	Follow-up for Patients Without Disease Progression[d]	Long Term Survival Follow-up[q]
	Days -28 to -1	D1	D15	D1	D2	D15/ D16	D1	D1				
Informed consent	X											
Study entry criteria	X											
Demographics	X											
Medical history	X											
Signs & symptoms/ Physical examination	X[e]	X[e,f]		X[f]			X[f]	X[f]	X[f]	X[e]		
ECOG performance status	X	X		X			X	X	X	X		
Vital signs	X	X[g]		X			X	X				
ECG	X	X[g]								X		
Coagulation[h]	X			X								
Hematology[h]	X	X[i]	X	X			X	X	X	X		
Clinical chemistry[h]	X	X[i]	X	X			X	X	X	X		
Serum lipids and creatine phosphokinase (CPK)	X	X[i]		X			X	X	X	X		
Thyroid Function Tests[h]	X						X	X[h]				
Other Endocrinology[h]	X			X				Cycle 4 only				
PSA[i]	X	X[i]		X			X	X	X		X	
CTC enumeration	X			X[j]			X[j]	Cycles 4 and 7 only[j]	X[j]		X	
CT/MRI	X			See footnote k					X		X	
Bone Scan	X			See footnote k					X		X	
Blood sample for PK		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]					
[redacted]												

[redacted]

Cobicistat administration	See footnote n											
CPI-1205 administration		See footnote o										
Abiraterone **OR** enzalutamide administration[p]		See footnote p										
Patient diary				X			X	X	X			
[redacted]												
Adverse events	X	X	X	X	X[l]	X[l]	X	X	X	X		
Concomitant medications	X	X	X	X	X[l]	X[l]	X	X	X	X		
Survival status												X[q]

a. Screening assessments should be performed within 28 days prior to C1D1 unless otherwise noted. **NOTE:** in order to minimize the volume of blood collected during a single visit, all blood samples do not have to be collected on the same day during Screening. There is no window for visits during Cycles 1 and 2, however, clinical laboratory parameters (see Section 7.3.5.7) may be drawn within 48 hours prior to day of visit. Starting in Cycle 3, a window of ± 3 days will be applied to all clinic visits.

b. The End of Treatment Visit should occur ≤ 7 days after the last dose of CPI-1205 or partner drug in the control arm of any randomized phase 2 trial if the patient does not participate in the crossover. If the patient had all the end of treatment assessments completed ≤ 7 days prior to the last dose of CPI-1205 or partner drug, these assessments do not need to be repeated at the End of Treatment Visit. **NOTE:** CT/MRI and bone scan do not need to be repeated if completed ≤ 28 days prior to the last dose of CPI-1205 or partner drug. **NOTE:** At the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator) or SRE, patients randomized to the control arm of any randomized phase 2 study may be eligible to cross over to the combination arm once the decision is made to start another systemic treatment for prostate cancer (see Section 5.5.1). See Table 7-4for the Schedule of Events for the crossover.

c. The Safety Follow-up Visit should occur 30 days (± 10 days) after the last dose of CPI-1205 or partner drug in the control arm of any randomized phase 2 trial if the patient does not participate in the crossover. If a patient does cross over, see Table 7-4.

d. Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2), and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their disease evaluated by PSA, CT/MRI,bone scan and CTC enumeration (if study treatment is discontinued prior to the last scheduled CTC collection). PSA and CTCs will be measured and imaging will be performed at the End of Treatment Visit; CTC enumeration and subsequent imaging should follow the same schedule as if patient had continued on treatment as outlined in footnotes j and k, respectively, until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. After the End of Treatment Visit, PSA should be measured each time imaging is performed.

e. A complete physical examination (including height [Screening only] and weight) and a signs and symptoms assessment will be performed during Screening and at the Safety Follow-up Visit. Physical exam/signs and symptoms assessment do not need to be repeated on C1D1 if the Screening evaluations are conducted ≤ 3 days prior to C1D1. In this case, the Screening evaluations will be considered baseline.

f. Assessment of signs and symptoms and an abbreviated physical examination (including weight) will be performed on D1 of each cycle and at the End of Treatment Visit. For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease (e.g., chest pain or discomfort at rest or with activity or shortness of breath) and hypersensitivity reactions.

g. Obtained prior to dosing and at 3 h (± 30 min) after dosing on C1D1 for any study arm that includes CPI-1205; for any control arm that includes only enzalutamide or abiraterone/prednisone, obtain prior to dosing only. Subsequent ECGs will only be performed during treatment if clinically indicated.

h. Hematology: complete blood count (CBC) with differential (includes hemoglobin, total white blood cell (WBC) count, differential WBC count, and platelet count).
Serum Chemistries: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, albumin, AST, ALT, lactate dehydrogenase (LDH), uric acid, calcium, magnesium, phosphate, serum glucose.
Coagulation Parameters: prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT)
Thyroid Function Tests: Thyroid stimulating hormone (TSH) and T4; to be collected at Screening, C3D1 and every other cycle thereafter
Other Endocrinology: sex hormone-binding globulin (SHBG), androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate, dihydrotestosterone (DHT), estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and total testosterone. **NOTE:** serum testosterone must be <50 ng/dL at Screening.

i. **NOTE:** C1D1 laboratory assessments must be reviewed and results must fulfill applicable inclusion criteria prior to initiation of dosing. If Screening assessment (other than PSA) was performed ≤ 3 days prior to C1D1, it does not need to be repeated C1D1. If Screening assessment for PSA was performed ≤ 7 days prior to C1D1, it does not need to be repeated C1D1. **NOTE:** PSA50 is defined as a ≥50% reduction in PSA from baseline. The reduction must be confirmed by a second PSA value 4 or more weeks later (see Section 10.1.2).

j. During treatment, after C4D1, repeat CTC on C7D1 only. A + 7 day window applies to all CTC collections during treatment. **NOTE:** Any CTC 30% response and any conversion from unfavorable to favorable CTC status must be confirmed by an additional CTC enumeration at least 4 weeks later (see Section 10.5).

k. CT/MRI and bone scan should be done during Screening, every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) until radiographic progression (as determined by the investigator). See Section 7.3.7.3 for additional details on the imaging procedures. **NOTE:** Changes in tumor measurements indicative of a response must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met (see Section 10.2.3). **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule. **NOTE:** At the time of unequivocal clinical progression, radiographic disease progression (as determined by the investigator), or SRE, patients randomized to the control arm of any randomized phase 2 study may be eligible to cross over to the combination arm once the decision is made to start another systemic treatment for prostate cancer (see Section 5.5.1).

l. In patients receiving CPI-1205 (with or without cobicistat), PK blood samples will be collected at the following timepoints: C1D1, C1D15 and C3D1 prior to the first dose of CPI-1205; C2D1 prior to the first dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients receiving CPI-1205 TID. AEs/concomitant medications will only be assessed on C2D2 for patients receiving CPI-1205. There will be no visit on C2D2 for patients on a control arm. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide, on C2D15 a PK blood sample will be collected prior to the morning dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients receiving CPI-1205 TID. AEs/concomitant medications will only be assessed on C2D15 and C2D16 for patients receiving enzalutamide. There will be no visit on C2D15 and C2D16 for patients receiving CPI-1205 (with or without cobicistat) + abiraterone/prednisone or for patients on a control arm. **NOTE:** In combination study arms only, the enzalutamide and/or abiraterone dose may be increased after Cycle 2 based on the specific patient's PK results and only after consultation with the Medical Monitor. If a dose increase is implemented, an additional blood sample for PK is required. See Sections 6.2.3 and 6.2.5.

m. [redacted]

[redacted]

n. During Screening, patients in study arms that include CPI-1205/cobicistat will be provided with oral cobicistat to be started the evening of day 0 and taken with food. Cobicistat will then be given BID starting on day 1 of CPI-1205, continuing throughout CPI-1205 dosing. Patients will be instructed on when and how to take this medication by the study staff. **NOTE:** Site staff will call each patient within 24 hours prior to C1D1 to remind patient to take cobicistat as instructed.
o. Patients enrolled in any phase 2 study arm that incorporates CPI-1205 will receive CPI-1205 orally at the RP2D.
p. Patients enrolled in any phase 2 study arm that includes enzalutamide will receive enzalutamide orally, once daily. Patients enrolled in any phase 2 study arm that includes abiraterone/prednisone will receive abiraterone orally, once daily, plus prednisone orally BID (or with frequency of prednisone administration at the discretion of the investigator).
q. Long-term follow-up will begin after the Safety Follow-up Visit. All patients will be followed every 3 months for 2 years and then every 6 months until death or the study is closed to collect survival status. Contact can be conducted via telephone.

[redacted]

Table 7-4 Schedule of Events: Combination Arm after Crossover from Control Arm of Randomized Phase 2 Trial

NOTE: At the time any patient crosses over from the control arm to the combination arm, the first cycle of combination treatment will be considered Cycle 1.

NOTE: Patients must meet criteria as outlined in Section 5.5.1 prior to first dose of CPI-1205 with or without cobicistat. Treatment with the second generation androgen inhibitor may continue while patient is under evaluation for crossover eligibility.

NOTE: This schedule of events will also be used for patients in phase 1b Dose Level 1A (CPI-1205 PO TID without cobicistat) who switch to CPI-1205 PO BID with cobicistat. The first cycle of CPI-1205 PO BID with cobicistat will be considered Cycle 1.

Assessment	Cycle 1[a]		Cycle 2[a]			Cycle 3[a]	Cycles 4+[a]	End of Treatment Visit[b]	Safety Follow-up Visit[c]	Follow-up for Patients Without Disease Progression[d]	Long Term Survival Follow-up[q]
	D1	D15	D1	D2	D15/ D16	D1	D1				
Signs & symptoms/ Physical examination	X[e]		X[e]			X[e]	X[e]	X[e]	X[f]		
ECOG performance status	X		X			X	X	X	X		
Vital signs	X[g]		X			X	X				
ECG	X[g]								X		
Coagulation[h]			X								
Hematology[h]	X[i]	X	X			X	X	X	X		
Clinical chemistry[h]	X[i]	X	X			X	X	X	X		
Lipids and CPK	X[i]		X			X	X	X	X		
Thyroid Function Tests[h]	X					X	X[h]				
Other Endocrinology[h]			X				Cycle 4 only				
PSA[i]	X[i]		X			X	X	X		X	
CTC enumeration	X[k]		X[j]			X[j]	Cycles 4 and 7 only[j]			X	
CT/MRI	X			See footnote l				X		X	
Bone Scan	X			See footnote l				X		X	
Blood sample for PK	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]					
[redacted]											

[redacted]

Cobicistat administration	See footnote o										
CPI-1205 administration	See footnote p										
Abiraterone **OR** enzalutamide administration[q]	See footnote q										
Patient diary			X			X	X	X			
[redacted]											
Adverse events	X	X	X	X[m]	X[m]	X	X	X	X		
Concomitant medications	X	X	X	X[m]	X[m]	X	X	X	X		
Survival Status											X

a. There is no window for visits during Cycles 1 and 2, however, clinical laboratory parameters (see Section 7.3.5.7) may be drawn within 48 hours prior to day of visit. Starting in Cycle 3, a window of ± 3 days will be applied to all clinic visits.

b. The End of Treatment Visit should occur ≤ 7 days after the last dose of CPI-1205. If the patient had all the end of treatment assessments completed ≤ 7 days prior to the last dose of CPI-1205, these assessments do not need to be repeated at the End of Treatment Visit. **NOTE:** CT/MRI and bone scan do not need to be repeated if completed ≤ 28 days prior to the last dose of CPI-1205.

c. The Safety Follow-up Visit should occur 30 days (± 10 days) after the last dose of CPI-1205.

d. Patients who discontinue study treatment for reasons other than radiographic progression will continue to have their disease evaluated by PSA, CT/MRI,bone scan and CTC enumeration (if study treatment is discontinued prior to the last scheduled CTC collection). PSA and CTCs will be measured and imaging will be performed at the End of Treatment Visit; CTC enumeration and subsequent imaging should follow the same schedule as if patient had continued on treatment as outlined in footnotes j and l, respectively, until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. After the End of Treatment Visit, PSA should be measured each time imaging is performed.

e. Assessment of signs and symptoms and an abbreviated physical examination (including weight) will be performed on D1 of each cycle and at the End of Treatment Visit. For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease (e.g., chest pain or discomfort at rest or with activity or shortness of breath) and hypersensitivity reactions.

f. A complete physical examination (including weight) and a signs and symptoms assessment will be performed at the Safety Follow-up Visit.

g. Obtained prior to dosing and at 3 h (± 30 min) after dosing on C1D1. Subsequent ECGs will only be performed during treatment if clinically indicated.

h. Hematology: complete blood count (CBC) with differential (includes hemoglobin, total white blood cell (WBC) count, differential WBC count, and platelet count). Serum Chemistries: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, albumin, AST, ALT, lactate dehydrogenase (LDH), uric acid, calcium, magnesium, phosphate, serum glucose.

Coagulation Parameters: prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT)
Thyroid Function Tests: Thyroid stimulating hormone (TSH) and T4; to be collected at Screening, C3D1 and every other cycle thereafter
Other Endocrinology: sex hormone-binding globulin (SHBG), androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate, dihydrotestosterone (DHT), estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and total testosterone.

i. **NOTE:** Patients must meet criteria as outlined in Section 5.5.1 prior to first dose of CPI-1205 with or without cobicistat. If hematology, clinical chemistry, serum lipids and creatine phosphokinase were performed ≤ 3 days prior to C1D1, they do not need to be repeated C1D1. If PSA was performed ≤ 7 days prior to C1D1, it does not need to be repeated C1D1. **NOTE:** PSA50 is defined as a ≥50% reduction in PSA from baseline. The reduction must be confirmed by a second PSA value 4 or more weeks later (see Section 10.1.2).

j. During treatment, after C4D1, repeat CTC on C7D1 only. A+ 7 day window applies to all CTC collections during treatment. **NOTE:** Any CTC 30% response and any conversion from unfavorable to favorable CTC status must be confirmed by an additional CTC enumeration at least 4 weeks later (see Section 10.5).

k. Collect predose

l. CT/MRI and bone scan should be done prior to the first dose of CPI-1205 (unless completed ≤ 14 days prior to the start of CPI-1205) and then every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) until radiographic progression (as determined by the investigator). See Section 7.3.7.3 for additional details on the imaging procedures. **NOTE:** Changes in tumor measurements indicative of a response must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met (see Section 10.2.3). **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule.

m. For patients who crossover from the control arm of a randomized phase 2 trial:
PK blood samples will be collected at the following timepoints: C1D1, C1D15 and C3D1 prior to the first dose of CPI-1205; C2D1 prior to the first dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients receiving CPI-1205 TID. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide, on C2D15 a PK blood sample will be collected prior to the morning dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min), 6 h (± 15 min), and 24 h (± 3 h). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients receiving CPI-1205 TID. AEs/concomitant medications will only be assessed on C2D15 and C2D16 for patients receiving enzalutamide. There will be no visit on C2D15 and C2D16 for patients receiving CPI-1205 (with or without cobicistat) + abiraterone/prednisone. **NOTE:** The enzalutamide and/or abiraterone dose may be increased after Cycle 2 based on the specific patient's PK results and only after consultation with the Medical Monitor. If a dose increase is implemented, an additional blood sample for PK is required. See Sections 6.2.3 and 6.2.5.

For patients who switch from CPI-1205 TID to CPI-1205 BID with cobicistat:
PK blood samples will be collected at the following timepoints: C1D1 and C2D1 prior to the first dose of CPI-1205 and at the following time points after dosing: 30 min (± 10 min), 1 h (± 15 min), 2 h (± 15 min), 3 h (± 15 min), 4 h (± 15 min), 5 h (± 15 min) and 6 h (± 15 min). A blood sample for PK will also be collected on C1D15 prior to the first dose of CPI-1205. There will be no visit required on C2D2, C2D15 or C2D16. **NOTE:** The enzalutamide and/or abiraterone dose may be increased after Cycle 2 based on the specific patient's PK results and only after consultation with the Medical Monitor. If a dose increase is implemented, an additional blood sample for PK is required. See Sections 6.2.3 and 6.2.5.

n. [redacted]

o. During evaluation for crossover (see Section 5.5.1), if the regimen includes cobicistat, patients will be provided with oral cobicistat to be started the evening of day 0 and taken with food. Cobicistat will then be given BID starting on day 1 of CPI-1205, continuing throughout CPI-1205 dosing. Patients will be instructed on when and how to take this medication by the study staff. **NOTE:** Site staff will call each patient within 24 hours prior to C1D1 to remind patient to take cobicistat as instructed.

p. Patients who cross over from the control arm of a randomized phase 2 will receive CPI-1205 orally at the RP2D. For patients who switch from CPI-1205 TID to CPI-1205 BID with cobicistat, the dose of CPI-1205 will be determined by the Medical Monitor. Patients enrolled in any study arm that includes enzalutamide will receive enzalutamide orally, once daily. Patients enrolled in any study arm that includes abiraterone/prednisone will receive abiraterone orally, once daily, plus prednisone orally BID (or with frequency of prednisone administration at the discretion of the investigator).
q. Long-term follow-up will begin after the Safety Follow-up Visit. All patients will be followed every 3 months for 2 years and then every 6 months until death or the study is closed to collect survival status. Contact can be conducted via telephone.

7.2 Schedule of Events Summary by Study Period

7.2.1 Screening Procedures for Tables 7-1 (Phase 1b Dose Escalation), 7-2 (Phase 1b HPEC[s]), 7-3 (Phase 2; randomized or single-arm)

During the 28 days prior to C1D1 (unless otherwise noted), the following Screening procedures will be performed. **NOTE:** in order to minimize the volume of blood collected during a single visit, all blood samples do not have to be collected on the same day during Screening:

- Review and sign ICF
- Review inclusion/exclusion criteria for patient eligibility
- Obtain patient demographics and detailed medical history, including any previous BReast CAncer genes (BRCA)/Homologous Recombination Deficiency (HRD) results [redacted]
- Perform a complete physical examination (including height and weight) and assess signs and symptoms
- Evaluate ECOG performance status
- Obtain vital signs
- Perform ECG
- Obtain coagulation, hematology, clinical chemistry, lipids, CPK, thyroid function tests and other endocrinology labs
- Measure PSA for baseline disease evaluation
- Collect blood for CTC enumeration
- Perform CT/MRI and bone scan for baseline disease evaluation
- [redacted]
- [redacted]
- Request archival tissue
- Record all concomitant medications
- Assess for baseline AEs
- Provide oral cobicistat with instructions for start on the evening of day 0 (taken with food) prior to C1D1 to any patient enrolled in a cohort/study arm that includes CPI-1205/cobicistat.
    - Call each patient scheduled to start CPI-1205/cobicistat within 24 hours prior to C1D1 to remind patient to take cobicistat as instructed.

[redacted]

7.2.2 Treatment Procedures for Tables 7-1 (Phase 1b Dose Escalation), 7-2 (Phase 1b HPEC[s]) and 7-3 (Phase 2; randomized or single-arm)

NOTE: C1D1 laboratory assessments must be reviewed and results must fulfill applicable inclusion criteria prior to initiation of dosing of CPI-1205. If Screening physical exam/signs and symptoms, hematology and clinical chemistry labs, lipids and CPK were performed within 3 days of C1D1, they do not need to be repeated on C1D1. If PSA was collected within 7 days of C1D1 it does not need to be repeated on C1D1.

All visits during Cycles 1 and 2 must be performed on the specified visit day. However, clinical laboratory parameters (see Section 7.3.5.7) may be drawn within 48 hours prior to day of visit. All other clinic visits during treatment may be performed ± 3 days of the specified visit day. The following procedures will be conducted during treatment:

- Perform an abbreviated physical examination (including weight) and assess signs and symptoms on D1 of each cycle (**NOTE:** For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease [e.g., chest pain or discomfort at rest or with activity or shortness of breath] and hypersensitivity reactions)
- Evaluate ECOG performance status on D1 of each cycle
- Obtain vital signs on D1 of each cycle; on C1D1, vital signs are collected pre-dose and 3 h (± 30 min) after dosing for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, obtain pre-dose only.
- Perform ECG prior to dosing and 3 h (± 30 min) after dosing on C1D1 for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, obtain pre-dose only. Subsequent ECGs will only be performed during treatment if clinically indicated.
- Obtain hematology and clinical chemistry labs on D1, D8, D15 and D22 of Cycle 1, on D1 and D15 of Cycles 2 and 3, and D1 of Cycles 4+ in phase 1b dose escalation cohorts; D1 and D15 of Cycle 1, on D1 of Cycles 2+ in phase 1b HPEC(s) and phase 2.
- Obtain lipids and CPK on D1 of each cycle
- Obtain coagulation labs on C2D1
- Obtain other endocrinology labs on C2D1 and C4D1; obtain thyroid function tests on C3D1 and every other cycle thereafter (i.e., C5D1, C7D1, etc.)
- Measure PSA on D1 of each cycle

- Collect blood for CTC enumeration on C2D1, C3D1, C4D1 and C7D1. **NOTE**: a window of +7 days applies to all CTC collections.
- Perform CT/MRI and bone scan every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles). **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule.
- In all patients enrolled in phase 1b dose escalation, collect blood for PK on C1D1 (24-hour collection on C1D2), C1D15 (24-hour collection on C1D16), C2D1 (24-hour collection on C2D2) and C4D1 (24-hour collection on C4D2). In addition, collect blood for PK prior to dosing on C1D8 and C1D22. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide only in phase 1b dose escalation, collect blood for PK on C2D15 (24-hour collection on C2D16). For consenting* patients enrolled in the phase 1b HPEC, collect blood for PK prior to dosing on C1D1 and C1D15, on C2D1 (24-hour collection on C2D2), and pre-dose on C3D1. For patients receiving CPI-1205 + enzalutamide only, also collect blood for PK on C2D15 (24-hour collection on C2D16). *PK sampling will be required in at least 10 patients enrolled in each HPEC. In phase 2 and only in study arm(s) that include CPI-1205, collect blood for PK on pre-dose on C1D1 and C1D15, C2D1 (24-hour collection on C2D2), and pre-dose on C3D1. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide only, collect blood for PK on C2D15 (24-hour collection on C2D16).

[redacted]

- Review patient diary D1 of each cycle (starting with Cycle 2)

[redacted]

- Record all concomitant medications at each visit
- Assess for AEs at each visit

7.2.3 Treatment Procedures for Table 7-4 (Combination Arm after Crossover)

NOTE: Patients must meet criteria outlined in Section 5.5.1 to be eligible for crossover. This requires that hematology and clinical chemistry lab results be available prior to initiation of dosing of CPI-1205 (with or without cobicistat).

NOTE: At the time any patient crosses over from the control arm to a combination arm, the first cycle of combination treatment will be considered Cycle 1.

NOTE: These procedures will also be followed for patients in phase 1b Dose Level 1A (CPI-1205 PO TID without cobicistat) who switch to CPI-1205 PO BID with cobicistat. The first cycle of CPI-1205 PO BID with cobicistat will be considered Cycle 1.

If hematology, clinical chemistry, serum lipids and creatine phosphokinase were performed ≤ 3 days prior to C1D1, they do not need to be repeated C1D1. If PSA was performed ≤ 7 days prior to C1D1, it does not need to be repeated C1D1.

All visits during Cycles 1 and 2 must be performed on the specified visit day. However, clinical laboratory parameters (see Section 7.3.5.7) may be drawn within 48 hours prior to day of visit. All other clinic visits during treatment may be performed ± 3 days of the specified visit day. The following procedures will be conducted during treatment:

- For patients on cobicistat, provide oral cobicistat with instructions for start on the evening of day 0 (taken with food) prior to C1D1.
    - Call each patient scheduled to start cobicistat within 24 hours prior to C1D1 to remind patient to take cobicistat as instructed.
- Perform an abbreviated physical examination (including weight) and assess signs and symptoms on D1 of each cycle (**NOTE:** For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease [e.g., chest pain or discomfort at rest or with activity or shortness of breath] and hypersensitivity reactions)
- Evaluate ECOG performance status on D1 of each cycle
- Obtain vital signs on D1 of each cycle; on C1D1, vital signs are collected pre-dose and 3 h (± 30 min) after dosing
- Perform ECG prior to dosing and 3 h (± 30 min) after dosing on C1D1. Subsequent ECGs will only be performed during treatment if clinically indicated.
- Obtain hematology and clinical chemistry labs on D1 and D15 of Cycle 1 and D1 of Cycles 2+
- Obtain lipids and CPK on D1 of each cycle
- Obtain coagulation labs on C2D1
- Obtain other endocrinology labs on C2D1 and C4D1; obtain thyroid function tests on C1D1, C3D1 and every other cycle thereafter (i.e., C5D1, C7D1, etc.)

- Measure PSA on D1 of each cycle
- Collect blood for CTC enumeration prior to treatment on C1D1, C2D1, C3D1, C4D1 and C7D1. **NOTE:** a window of +7 days applies to all CTC collections.
- Perform CT/MRI and bone scan prior to the first dose of CPI-1205 (unless completed ≤ 14 days prior to the start of CPI-1205) and then every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles); **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule.
- **For patients who crossover from the control arm of a randomized phase 2 trial:** Collect blood for PK pre-dose on C1D1 and C1D15, on C2D1 (24-hour collection on C2D2), and pre-dose on C3D1. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide only, collect blood for PK on C2D15 (24-hour collection on C2D16).

  For patients who switch from CPI-1205 TID to CPI-1205 BID with cobicistat: Collect blood for PK on C1D1 (through 6 hours post dose), pre-dose on C1D15 and on C2D1 (through 6 hours post dose).
- [redacted]
- [redacted]
- Review patient diary D1 of each cycle (starting with Cycle 2)

[redacted]

- Record all concomitant medications at each visit

- Assess for AEs at each visit

[redacted]

7.2.4 End of Treatment Visit for Tables 7-1, 7-2, 7-3 and 7-4 (all enrolled patients)

The End of Treatment Visit should occur ≤ 7 days after the last dose of CPI-1205 or partner drug for the control arm of a randomized phase 2 study if the patient does not participate in the crossover. If the patient had all the end of treatment assessments completed ≤ 7 days prior to the last dose of CPI-1205 or partner drug, these assessments do not need to be repeated at the End of Treatment Visit. **NOTE:** CT/MRI and bone scan do not need to be repeated if completed ≤ 28 days prior to the last dose of CPI-1205 or partner drug.

The following procedures will be conducted at the End of Treatment Visit:

- Perform an abbreviated physical examination (including weight) and assess signs and symptoms (**NOTE:** For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease [e.g., chest pain or discomfort at rest or with activity or shortness of breath] and hypersensitivity reactions)
- Evaluate ECOG performance status
- Obtain hematology and clinical chemistry labs
- Obtain lipids and CPK
- Collect blood for CTC enumeration
- Measure PSA
- Perform CT/MRI and bone scan**; NOTE:** CT/MRI and bone scan do not need to be repeated if completed ≤ 28 days prior to the last dose of CPI-1205 or partner drug
- Review patient diary

[redacted]

- Record all concomitant medications
- Assess for AEs

7.2.5 Safety Follow-up Visit for Tables 7-1, 7-2, 7-3 and 7-4 (all enrolled patients)

The Safety Follow-up Visit should occur 30 days (± 10 days) after the last dose of CPI-1205 or partner drug for the control arm of a randomized phase 2 study if the patient does not participate in the crossover (**NOTE:** if patient does cross over, then the Safety Follow-up Visit should take place 30 days (± 10 days) after the last dose of CPI-1205).

The following procedures will be conducted at the Safety Follow-up Visit:

- Perform a complete physical examination (including weight) and assess signs and symptoms
- Evaluate ECOG performance status
- Perform ECG
- Obtain hematology and clinical chemistry labs
- Obtain lipids and CPK
- [redacted]
- Record all concomitant medications
- Assess for AEs

If patients refuse to come in for the Safety Follow-up Visit, they will be contacted by phone for 30 days (± 10 days) after the last dose of CPI-1205 to assess safety.

7.2.6 Long Term Survival Follow-up for HPEC(s) and Phase 2 (Tables 7-2, 7-3 and 7-4)

Long-term follow-up will begin after the Safety Follow-up Visit. All patients enrolled in a HPEC will be followed every 3 months until death or the study is closed to collect survival status. All patients enrolled in phase 2 will be followed every 3 months for 2 years and then every 6 months until death or the study is closed to collect survival status. Contact can be conducted via telephone.

7.2.7 Follow-up for Patients without Disease Progression for Tables 7-1, 7-2, 7-3 and 7-4 (all enrolled patients)

Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2) and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their disease evaluated by PSA, CT/MRI,bone scan and CTC enumeration (if study treatment is discontinued prior to the last scheduled CTC collection). PSA and CTCs will be measured and imaging will be performed at the End of Treatment Visit.

Subsequent imaging and CTC enumeration should follow the same schedule as outlined in the respective Schedule of Events for the applicable cohort as if patient had continued on treatment until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. After the End of Treatment Visit, PSA should be measured each time imaging is performed. **NOTE:** if patients in a cohort/study arm that includes both CPI-1205 (with or without cobicistat) and a partner drug come off of protocol mandated therapy (see Section 6.2), but the treating physician decides to continue either single agent abiraterone or enzalutamide off protocol, this will not be considered a "new" anti-cancer treatment.

7.2.8 Post End-of-Study for Tables 7-1, 7-2, 7-3 and 7-4 (all enrolled patients)

Following the end of the study, no further medical care or treatment will be provided to patients through this study by the study investigator(s). Thereafter, patients will receive medical care at the discretion of their physician. If a new event occurs after the termination of the trial that is likely to change the risk/benefit analysis of the trial and could still have an impact on the trial participants, the sponsor should notify the competent authority and ethics committees concerned and provide a proposed course of action.

7.3 Details on Study Procedures

NOTE: At the time any patient crosses over from the control arm to a combination arm in a randomized phase 2 trial (or a patient in phase 1b Dose Level 1A switches from CPI-1205 TID to CPI-1205 BID with cobicistat), the first cycle of combination treatment (or the first cycle of CPI-1205 BID with cobicistat) will be considered Cycle 1, and the schedules included in the sections below apply.

7.3.1 Informed consent

Each patient must provide written informed consent before any study-related procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.3.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during Screening (≤ 28 days before C1D1 unless otherwise noted in Section 7.2.1).

7.3.3 Demographics

Patient demographics will be documented during Screening and will include patient birth date, gender, and race.

7.3.4 Medical History

During the Screening period, the patient will have a complete medical history taken including:

- All previous lines of therapy for the treatment of prostate cancer (represented as a single agent or combination and to include AR inhibitors, radium-223, sipuleucel-T,

chemotherapy, investigational agents (e.g., PARP inhibitor), and any other medications/therapies used to treat prostate cancer) should be recorded in the order they were administered. Ideally, reporting should include the start and stop dates (or at least the duration) for each prior line of therapy, the dose and schedule of the agent(s) administered, the disease state in which it was administered (i.e., metastatic hormone sensitive, non-metastatic CRPC, mCRPC), and the type of progression (biochemical [i.e., a rising PSA], radiographic, and/or symptomatic). The best outcome (for PSA and soft tissue if applicable) for each prior line of therapy should be documented. **NOTE:** if available, baseline and post treatment PSA for any line of previous treatment for mCRPC should be documented.

- Details on prior radiation therapy should be recorded, including those directed at the primary and metastatic site(s). Details should include dates, portals, number of fractions, dose per fraction, and total administered dose by portal. Details of prior radioisotope therapy should also be recorded.
- Type of progression on entry should be recorded (i.e., progression based on PSA, soft tissue and/or bone). Specifically, it should be noted whether progression was by PSA alone, bone ± nodes by location, nodes by location only, or viscera (± other sites). For soft tissue progression, it should be noted whether progression was due to growth of pre-existing lesions, the development of new lesions, or both.
- Document any previous BRCA/HRD results [redacted]

7.3.5 Safety Assessments

7.3.5.1 Adverse Events

AEs will be monitored and recorded throughout the study period, beginning from the time of informed consent and for 30 days following the last dose of CPI-1205 or partner drug for patients on the control arm of any randomized phase 2 study who do not participate in the crossover. All AEs considered at least possibly related to study treatment (see Section 12.2.3) and all serious adverse events (SAEs) that occur during the reporting period will continue to be followed until the event resolves, the investigator assesses the event as stable, the event is determined to be irreversible, or the patient is lost to follow-up. Definitions, documentation, and reporting of AEs are described in detail in Section 12.

7.3.5.2 ECOG Performance Status

ECOG performance status (see Appendix 1) will be assessed during Screening, on D1 of each cycle, at the End of Treatment Visit, and at the Safety Follow-up Visit.

7.3.5.3 Signs & Symptoms/Physical Examination

An assessment of signs and symptoms and a complete physical examination will be conducted during Screening and at the Safety Follow-up Visit. The Screening physical examination will record the patient's height and weight, the Safety Follow-up Visit physical examination will record weight only.

An assessment of signs and symptoms and an abbreviated physical examination (directed toward the identification of signs of treatment-related toxicity and disease progression or regression) including the patient's weight, will be performed D1 of each cycle and at the End of Treatment Visit.

NOTE: special attention to be paid to identification of SREs and SSEs as defined in Section 10.6 and any signs of unequivocal clinical progression (see Section 10.4).

NOTE: For patients receiving enzalutamide, special attention should be paid to any signs/symptoms of ischemic heart disease (e.g., chest pain or discomfort at rest or with activity or shortness of breath) and hypersensitivity reactions.

A physical exam and signs and symptoms assessment do not need to be repeated on C1D1 if the Screening evaluations are conducted ≤ 3 days prior to C1D1. In this case, the Screening evaluations will be considered baseline.

7.3.5.4 Vital Signs

Vital signs (BP, heart rate, and oral temperature) will be taken during Screening and on D1 of each cycle of treatment.

On C1D1, vital signs will be taken prior to dosing, and will be repeated 3 h (± 30 min after dosing for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, obtain pre-dose only.

7.3.5.5 Electrocardiograms

A 12-lead ECG will be obtained as part of the Screening evaluation.

On C1D1, an ECG will be performed prior to dosing, and will be repeated 3 h (±30 min) after dosing for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, obtain pre-dose only. Subsequent ECGs will only be performed during treatment if clinically indicated. ECG will also be performed at the Safety Follow-Up Visit.

7.3.5.6 Concomitant Medications and Supportive Therapies

All concomitant medications and supportive therapies will be recorded from Screening through the Safety Follow-up Visit. Concomitant medications and therapies that are prohibited or to be used with caution are described in Section 6.3, Appendix 4 and Appendix 5.

7.3.5.7 Clinical Laboratory Evaluations

If hematology, clinical chemistry, lipids and CPK labs were performed within 3 days of C1D1, they do not need to be repeated on C1D1. **NOTE:** C1D1 laboratory assessments must be reviewed and results must fulfill applicable inclusion criteria prior to initiation of dosing. During any subsequent visit in Cycle 1 and for any Cycle 2 visit, blood for these evaluations may be drawn within 48 hours prior to day of visit.

COAGULATION PARAMETERS

Prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT) will be determined during Screening for all patients. Subsequent measurement of the PT/INR and aPTT will be performed on D1 of Cycle 2 and thereafter only as clinically indicated.

HEMATOLOGY

A complete blood count (CBC) with differential will be obtained during Screening, on D1, D8, D15 and D22 of Cycle 1, on D1 and D15 of Cycles 2 and 3, on D1 of Cycles 4+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 1b dose escalation, during Screening, on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 1b HPEC(s) and phase 2, and on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit after crossover.

The CBC with differential consists of the following: hemoglobin, total WBC count, differential WBC count, and platelet count.

CLINICAL CHEMISTRY

A clinical chemistry panel will be obtained during Screening, on D1, D8, D15 and D22 of Cycle 1, on D1 and D15 of Cycles 2 and 3, on D1 of Cycles 4+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 1b dose escalation, during Screening, on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 1b HPEC(s) and phase 2 and during on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit after crossover.

The clinical chemistry panel consists of the following: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, albumin, AST, ALT, lactate dehydrogenase (LDH), uric acid, calcium, magnesium, phosphate, serum glucose.

SERUM LIPIDS AND CREATINE PHOSPHOKINASE (CPK)

Serum lipids and CPK will be obtained during Screening, on D1 of each cycle, at the End of Treatment Visit and at the Safety Follow-up Visit in all patients.

Serum lipids will include total cholesterol, cholesterol low density lipoprotein (LDL), cholesterol high density lipoprotein (HDL) and triglycerides.

THYROID FUNCTION TESTS

Thyroid function tests include thyroid stimulating hormone (TSH) and T4 will be obtained at Screening, on C3D1, and every other subsequent cycle (i.e., C5D1, C7D1, etc.) during phase 1b (all cohorts) and phase 2. After crossover, thyroid function tests will be obtained on C1D1, C3D1 and every other cycle thereafter (i.e., C5D1, C7D1, etc.).

OTHER ENDOCRINOLOGY

Other endocrinology labs will be obtained at Screening, on C2D1, and on C4D1 in all patients.

Endocrinology labs include: sex hormone-binding globulin (SHBG), androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate, dihydrotestosterone (DHT), estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin and total testosterone.

NOTE: At Screening, serum testosterone must be <50 ng/dL (i.e., patient must meet the definition for castrate).

7.3.6 Patient Diary [redacted]

7.3.6.1 Patient Diary

Patients will receive diaries that include the instructions for home administration of CPI-1205, cobicistat (if applicable) and abiraterone **OR** enzalutamide and a log to record the date and time of each dose as well as the number and strength (mg) of capsules or tablets taken, and the reason for any missed doses. Detailed instructions for completion and review of the diaries will be provided in the study manual.

The study center staff will review the patient's diary on D1 of each cycle (staring Cycle 2) and at the End of Treatment Visit.

[redacted]

7.3.7 Disease Evaluation Procedures

Details on disease response assessment are provided in Section 10.

7.3.7.1 PSA

PSA will be measured at Screening, on D1 of each cycle and at the End of Treatment Visit in all patients. Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2) and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their disease evaluated by PSA on the same schedule as imaging (see Sections 7.3.7.3 and 7.3.7.4) until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first.

NOTE: If the PSA was done within 7 days of C1D1, it does not need to be repeated on C1D1.

7.3.7.2 Enumeration of CTCs

For phase 1b (all cohorts) and phase 2, 7.5 mL of blood will be collected during Screening, on C2D1, C3D1, C4D1, C7D1 and at the End of Treatment Visit for CTC enumeration. For the crossover, 7.5 mL of blood will be collected predose on C1D1, and on C2D1, C3D1, C4D1, C7D1 and at the End of Treatment Visit for CTC enumeration. **NOTE:** a + 7 day window applies to all CTC collections during treatment. Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2) and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their CTCs measured (if study treatment is discontinued prior to the last scheduled CTC collection) as if patient had continued on treatment as per the respective Schedule of Events until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first.

7.3.7.3 CT/MRI

For phase 1b and phase 2, CT/MRI should be done during Screening, every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) and at the End of Treatment Visit. For the crossover, CT/MRI should be done prior to the first dose of CPI-1205 (unless completed ≤ 14 days prior to the start of CPI-1205), every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) and at the End of Treatment Visit. **NOTE:** CT/MRI does not need to be repeated at the End of Treatment Visit if completed ≤ 28 days prior to the last dose of CPI-1205. Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2) and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their disease evaluated as if patient had continued on treatment as per the respective Schedule of Events until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule.

Imaging of the chest, abdomen, and pelvis using a CT scan with contrast with ≤ 5 mm axial slices is advised for all patients. For those intolerant of contrast, a cross-sectional MRI scan of the abdomen and pelvis, with a noncontrast CT scan of the chest, may be considered.

If appropriate CT/MRI scans were performed before the patient's screening for the study began, but were obtained ≤ 28 days before C1D1, then those scans may be used as the baseline scans.

Specific imaging of the prostate or prostate bed is not required for every patient. If there is a question of locally persistent or recurrent disease, a directed MRI of the prostate or prostate bed (and/or biopsy of the site) is recommended. If a patient develops symptoms of neurologic compromise during the trial, an MRI of the spine and base of the skull is recommended.

All measurements will be recorded in metric notation by use of a ruler, caliper, or by means of appropriate computer software. The same method of assessment and technique that were used for the baseline assessment of the patient's disease before treatment should be used for all subsequent response assessments in the study.

Imaging data (imaging studies and derived assessments) from phase 1b dose escalation will be stored according to usual practice by the sites and will be available upon request for review by the Sponsor or an independent radiology reviewer. For the HPEC(s) and for any phase 2 trial conducted, sites will be required to submit all radiographic imaging for CRR. Details on the CRR will be provided in a CRR charter, provided as a document separate from the protocol.

7.3.7.4 Bone Scan

In phase 1b and phase 2, a bone scan (^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy) should be done during Screening, every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) and at the End of Treatment Visit. For the crossover, a bone scan should be done prior to the first dose of CPI-1205 (unless completed ≤ 14 days prior to the start of CPI-1205), every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) and at the End of Treatment Visit. **NOTE:** bone scan does not need to be repeated at the End of Treatment Visit if completed ≤ 28 days prior to the last dose of CPI-1205. Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2) and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their disease evaluated as if patient had continued on treatment as per the respective Schedule of Events until another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first. **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule.

If appropriate bone scan was performed before the patient's screening for the study began, but was obtained ≤ 28 days before C1D1, then that scan may be used as the baseline scan.

Imaging data (imaging studies and derived assessments) from phase 1b dose escalation will be stored according to usual practice by the sites and will be available upon request for review by the Sponsor or an independent radiology reviewer. For the HPEC(s) and for any phase 2 trial conducted, sites will be required to submit all radiographic imaging for CRR. Details on the CRR will be provided in a CRR charter, provided as a document separate from the protocol.

[redacted]

7.3.8 Pharmacokinetic Measurements

7.3.8.1 Overview of the Pharmacokinetic Sampling Strategy

Serial peripheral blood samples (approximately 4 mL each) will be drawn before and after dosing in order to determine circulating concentrations of CPI-1205, cobicistat, and enzalutamide or abiraterone. In phase 1b dose escalation, serial peripheral blood sampling for PK will occur before and over the 24 hours following dosing on C1D1, C1D15, C2D1 and C4D1. A blood sample for PK will also occur prior to dosing on C1D8 and C1D22. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide, serial PK sampling will also occur before and over the 24 hours following dosing on C2D15. From consenting* patients enrolled in a phase 1b HPEC, a blood sample for PK will occur prior to dosing on C1D1, C1D15 and C3D1. Serial peripheral blood sampling for PK will occur before and over the 24 hours following dosing on C2D1. For patients receiving CPI-1205 + enzalutamide, serial PK sampling will also occur before and over the 24 hours following dosing on C2D15. *PK sampling will be required in at least 10 patients enrolled in each HPEC.

During phase 2 and in the combination arm(s) only, a blood sample for PK will occur prior to dosing on C1D1, C1D15 and C3D1. Serial peripheral blood sampling for PK will occur before and over the 24 hours following dosing on C2D1. For patients receiving CPI-1205 (with or without cobicistat) + enzalutamide, serial PK sampling will also occur before and over the 24 hours following dosing on C2D15. **NOTE:** This same schedule will be followed for patients in a randomized phase 2 control arm who participate in the crossover.

For Patients in Phase 1b Dose Level 1A (CPI-1205 PO TID without cobicistat) who switch to CPI-1205 PO BID with cobicistat, serial peripheral blood sampling for PK will occur before and over the 6 hours following dosing on C1D1 and C2D1. A blood sample will also be collected prior to dosing on C1D15.

The PK parameters to be estimated are AUC_{last}, C_{max}, T_{max}, C_{trough}, peak-to-trough ratio, and accumulation ratio (for both C_{max} and AUC_{last}).

[redacted]

7.3.8.2 Specific Time Points for Pharmacokinetic Sampling for Phase 1b Dose Escalation

The PK sampling time points are shown in Table 7-5. A total of approximately 188 mL of blood will be taken for pharmacokinetic samples for patients receiving CPI-1205 (with or without cobicistat) + enzalutamide. A total of approximately 152 mL of blood will be taken for pharmacokinetic samples for patients receiving CPI-1205 (with or without cobicistat) + abiraterone/prednisone. **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected in patients who are on CPI-1205 PO TID.

Table 7-5 Pharmacokinetic Sampling Schedule for Phase 1b Dose Escalation

Cycle Day	Time point	Total approximate amount of blood per study day
C1D1	• Prior to dosing • 30 minutes (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 mins) after dosing • 24 hours (± 3 hours) after C1D1 dosing and prior to C1D2 dosing	36 mL
C1D8	• Prior to dosing	4mL
C1D15	• Prior to dosing • 30 min (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 min) after dosing • 24 hours (± 3 hours) after C1D15 dosing and prior to C1D16 dosing	36 mL
C1D22	• Prior to dosing	4 mL
C2D1	• Prior to dosing • 30 min (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing	36 mL

	• 6 hours (± 15 min) after dosing • 24 hours (± 3 hours) after C2D1 dosing and prior to C2D2 dosing	
C4D1	• Prior to dosing • 30 minutes (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 mins) after dosing • 24 hours (± 3 hours) after C4D1 dosing and prior to C4D2 dosing	36 mL
Patients on CPI-1205 (with or without cobicistat) + enzalutamide only		
C2D15	• Prior to dosing • 30 min (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 min) after dosing • 24 hours (± 3 hours) after C2D15 dosing and prior to C2D16 dosing	36 mL

The timing, but not the number (unless fewer) of blood samples drawn may be changed if the emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK.

Details regarding the collection, handling and shipping of samples are provided in the study laboratory manual.

7.3.8.3 Specific Time Points for Pharmacokinetic Sampling for Phase 1b HPEC[s], Phase 2 and After Crossover in A Randomized Phase 2

The PK sampling time points are shown in Table 7-6. The approximate volume of blood taken for PK samples for patients receiving CPI-1205 (with or without cobicistat) in combination with abiraterone will be 48 mLs in phase 1b (HPEC patients who consent to PK and in phase 2 and after crossover). For those on enzalutamide, approximately 84mLs will be collected (HPEC patients who consent to PK and in phase 2 and after crossover). **NOTE:** The second dose of CPI-1205 should be taken after the 6 hour PK sample is collected on C2D1 in patients who are on CPI-1205 PO TID.

There is no PK sampling for patients on control arm(s) in phase 2.

Table 7-6 Pharmacokinetic Sampling Schedule for Phase 1b HPEC(s), Phase 2 and After Crossover in A Randomized Phase 2

Cycle Day	Time point	Total approximate amount of blood per study day
C1D1	• Prior to dosing	4 mL
C1D15	• Prior to dosing	4 mL
C2D1	• Prior to dosing • 30 min (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 min) after dosing • 24 hours (± 3 hours) after C2D1 dosing and prior to C2D2 dosing	36 mL
C3D1	• Prior to dosing	4 mL
Patients on CPI-1205 (with or without cobicistat) + enzalutamide only		
C2D15	• Prior to dosing • 30 min (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 min) after dosing • 24 hours (± 3 hours) after C2D15 dosing and prior to C2D16 dosing	36 mL

The timing, but not the number (unless fewer) of blood samples drawn may be changed if the emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK.

Details regarding the collection, handling and shipping of samples are provided in the study laboratory manual.

7.3.8.4 Specific Time Points for Pharmacokinetic Sampling for for Patients in Phase 1b Dose Level 1A (CPI-1205 PO TID without Cobicistat) who Switch to CPI-1205 PO BID with Cobicistat

The PK sampling time points are shown in Table 7-7. Approximately 68 mL of blood will be collected in patients who switch from CPI-1205 TID to CPI-1205 BID with cobicistat.

Table 7-7 Pharmacokinetic Sampling Schedule for Patients in Phase 1b Dose Level 1A (CPI-1205 PO TID without Cobicistat) who Switch to CPI-1205 PO BID with Cobicistat

Cycle Day	Time point	Total approximate amount of blood per study day
C1D1	• Prior to dosing • 30 min (±10 min) after dosing • 1 hour (±15 min) after dosing	32 mL

	• 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 min) after dosing	
C1D15	• Prior to dosing	4 mL
C2D1	• Prior to dosing • 30 min (±10 min) after dosing • 1 hour (±15 min) after dosing • 2 hours (±15 min) after dosing • 3 hours (±15 min) after dosing • 4 hours (±15 min) after dosing • 5 hours (±15 min) after dosing • 6 hours (± 15 min) after dosing	32 mL

The timing, but not the number (unless fewer) of blood samples drawn may be changed if the emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK.

Details regarding the collection, handling and shipping of samples are provided in the study laboratory manual.

[redacted]

[redacted]

[redacted]

8 WITHDRAWAL OF PATIENTS FROM THE STUDY

Patients will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. Additionally, the sponsor may terminate the study.

CPI-1205 treatment is to be permanently discontinued as per Section 6.4.

The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Patient withdrew consent
- Refusal of treatment/patient request
- Protocol violation
- Lack of compliance or excessive deviations
- Loss to follow-up (after repeated attempts for >30 days have been made to contact the patient including letters sent by registered mail to the patient and designated alternate contact)
- Significant clinical deterioration
- Administrative reasons
- Intercurrent illness
- Death

Following withdrawal of consent to participate in this trial by a patient, no new information will be collected from that patient and added to the existing data or any database, if requested by the patient. However, every effort will be made to follow all patients for safety.

9 DRUG INFORMATION

9.1 CPI-1205

CPI-1205, an investigational agent currently in clinical trials, is a small molecule inhibitor of the catalytic activity of EZH2.

9.1.1 Formulation

[redacted]

9.1.2 Supplier and Labeling

CPI-1205 will be provided by Constellation Pharmaceuticals, Inc. CPI-1205 will be labeled and handled at the investigational site as open-label material. CPI-1205 labels will fulfill all requirements specified by relevant governing regulations. There will be no information about the patient on the label. The storage conditions for CPI-1205 will be provided on the label.

9.1.3 Dispensing

In accordance with the site's standard procedures for investigational study drugs, the site pharmacist will dispense the appropriate number of tablets to each patient at the beginning of each cycle. CPI-1205 will be administered only to eligible patients under supervision of the investigator or identified sub-investigator(s). Patients will receive a sufficient quantity of CPI-1205 for each treatment cycle at the beginning of the treatment cycle.

9.1.4 Storage, Handling, and Accountability

CPI-1205 must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the pharmacist and designated assistants have access. Upon receipt, CPI-1205 should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Tablets should remain in the bottle provided until they are dispensed to patients. [redacted]

Because this is an investigational agent, it should be handled with due care.

The Investigator or designee must maintain an accurate record of the shipment and dispensing of CPI-1205 in a drug accountability ledger. Information collected will include the following: applicable lot numbers and total drug administered in mg. Any discrepancy regarding the dose administered and the reason for the discrepancy will be documented in the source records and electronic case report form (eCRF). Drug accountability will be evaluated by the field monitor during site visits and at the completion of the study. All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed to do so by Constellation, the Investigator must not destroy any drug labels, or any partly used or unused drug supply. See Section 13.10 for additional information.

9.1.5 Adverse Events Associated with CPI-1205

See the latest version of the CPI-1205 IB and Section 1.3.3.3.

9.1.6 Compliance

Patients will receive diaries that include the instructions for home administration of CPI-1205 and a log to record the date and time of each dose as well as the number and strength (mg) of tablets taken and the reason for any missed doses. Detailed instructions for completion and review of the diaries will be provided in the study manual.

Patients will receive a sufficient quantity of CPI-1205 for each treatment cycle at the beginning of the treatment cycle. The study center staff will check the patient's diary versus the patient's supply of remaining CPI-1205 tablets at the Day 1 visit of each new treatment cycle and at the End of Treatment Visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

9.2 Cobicistat

Cobicistat is a CYP3A4 inhibitor indicated to increase systemic exposure of antiretroviral agents. Of note, in CPI-1205-201, cobicistat will be given with CPI-1205, and without concomitant antiretrovirals. Cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing) in combination with other antiretroviral

agents in the treatment of HIV-1 infection. See the most up to date version of the US cobicistat prescribing information for detailed information on this agent (www.tybost.com). Cobicistat is also a component of the FDA approved drugs Stribild® (comprised of cobicistat, elvitegravir, emtricitabine and tenofovir DF), Prezcobix® (comprised of cobicistat and darunavir) and Evotaz® (comprised of cobicistat and atazanavir), all indicated for the treatment of HIV-1. Cobicistat is included to increase the systemic exposure of HIV patients to elvitegravir, darunavir and atazanavir within the respective products.

9.2.1 Supplier and Labeling

See Pharmacy Manual, provided as a document separate from this protocol.

9.2.2 Dispensing

In accordance with the site's standard procedures for investigational study drugs, the site pharmacist will dispense the appropriate number of tablets to each patient at the beginning of each cycle. Prior to Cycle 1, the site pharmacist will dispense one dose to be administered on the evening of Day 0 prior to Day 1 of treatment with CPI-1205. Cobicistat will be administered only to eligible patients under supervision of the investigator or identified sub-investigator(s). Patients will receive a sufficient quantity of cobicistat for each treatment cycle at the beginning of the treatment cycle.

9.2.3 Storage, Handling, and Accountability

Cobicistat must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the pharmacist and designated assistants have access. Upon receipt, cobicistat should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Tablets should remain in the bottle provided until they are dispensed to patients. The bottles should be stored at the investigational site at room temperature (25°C; 77°F; excursions permitted to 15-30°C; 59-86°F). Additionally, patients should be instructed to keep their supply of tablets under similar conditions. Containers should be kept closed during storage.

The Investigator or designee must maintain an accurate record of the shipment and dispensing of cobicistat in a drug accountability ledger. Information collected will include the following: applicable lot numbers and total drug administered in mg. Any discrepancy regarding the dose administered and the reason for the discrepancy will be documented in the source records and eCRF. Drug accountability will be evaluated by the field monitor during site visits and at the completion of the study. All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed to do so by Constellation, the Investigator must not destroy any drug labels, or any partly used or unused drug supply. See Section 13.10 for additional information.

9.2.4 Compliance

Patients will receive diaries that include the instructions for home administration of cobicistat and a log to record the date and time of each dose as well as the number and strength (mg) of tablets taken. Detailed instructions for completion and review of the diaries will be provided in the study manual.

The study center staff will check the patient's diary at the Day 1 visit of each new treatment cycle and at the End of Treatment Visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

9.2.5 Summary of Adverse Events Associated with Cobicistat

When used in the treatment of HIV in combination with atazanavir, the most common adverse drug reactions (incidence ≥ 2% of patients, (Grades 2−4) are jaundice, rash, ocular icterus, nausea, diarrhea and headache.

9.2.5.1 Contraindications

Cobicistat is contraindicated when given concomitantly with sensitive substrates of CYP3A (i.e., those with a narrow therapeutic index). Concomitant use of these drugs is already prohibited during the conduct of this trial (see Section 16, Appendix 4). The concomitant use of colchicine is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions.

9.2.5.2 Warnings and Precautions

The following warnings and precautions that are associated with the use of cobicistat and that are **NOT** specific to its use in the HIV population (from the August 2017 prescribing information):

- **Effects on Serum Creatinine:** Cobicistat decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating cobicistat, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance. Dosage recommendations are not available for drugs that require dosage adjustments in cobicistat-treated patients with renal impairment. Consider alternative medications that do not require dosage adjustments in patients with renal impairment. Although cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL from baseline should be closely monitored for renal safety.

- **Risk of Serious Adverse Reactions due to Drug Interactions:**

    - Initiation of cobicistat, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A, or initiation of medications metabolized by CYP3A in patients already receiving cobicistat may increase plasma concentrations of

medications metabolized by CYP3A. Increased concentrations may lead to clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from higher exposures of concomitant medications.

- Initiation of medications that inhibit or induce CYP3A may respectively increase or decrease concentrations of cobicistat, which may lead to clinically significant adverse reactions from higher exposures of cobicistat.

- See Section 6.3.1 for additional information on rules/guidance for concomitant medications for patients on cobicistat.

9.3 Enzalutamide

Enzalutamide is an AR inhibitor indicated for the treatment of patients with CRPC. See the most up to date version of the US enzalutamide prescribing information for detailed information on this agent (www.xtandi.com).

9.3.1 Supplier

Commercial supplies of enzalutamide will be used and charged to the patient and/or his insurance company.

9.3.2 Compliance

Patients will receive diaries that include the instructions for home administration of enzalutamide and a log to record the date and time of each dose as well as the number and strength (mg) of capsules taken. Detailed instructions for completion and review of the diaries will be provided in the study manual.

The study center staff will check the patient's diary at the Day 1 visit of each new treatment cycle and at the End of Treatment Visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

9.3.3 Summary of Adverse Events Associated with Enzalutamide

The most common adverse reactions (≥10%) reported in the randomized placebo-controlled clinical trials of enzalutamide that occurred more commonly (≥2% over placebo) in the enzalutamide arm were asthenia/fatigue, decreased appetite, arthralgia, hot flush, weight decreased, headache, hypertension, and dizziness/vertigo.

The following warnings are associated with the use of enzalutamide (from the July 2018 prescribing information):

- **Seizure:** Seizure occurred in 0.4% of patients receiving enzalutamide in clinical studies in which patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 604 days after initiation of enzalutamide. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. In patients with predisposing factors, seizures were reported in 2.2% of patients in a single

arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizures. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor. It is unknown whether anti-epileptic medications will prevent seizures with enzalutamide. Because of the risk of seizure associated with enzalutamide use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue enzalutamide in patients who develop a seizure during treatment.

- **Posterior Reversible Encephalopathy Syndrome (PRES):** There have been reports of PRES in patients receiving enzalutamide. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue enzalutamide in patients who develop PRES.

- **Hypersensitivity:** Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in four randomized clinical trials, and pharyngeal edema has been reported in post-marketing cases. Patients who experience any symptoms of hypersensitivity should temporarily discontinue enzalutamide and promptly seek medical care. Enzalutamide should be permanently discontinued for serious hypersensitivity reactions.

- **Ischemic Heart Disease:** Across three randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the enzalutamide arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients on the enzalutamide arm compared to 0.5% on the placebo arm. Ischemic events led to death in 0.4% of patients on the enzalutamide arm compared to 0.1% on the placebo arm. Patients should be monitored for signs and symptoms of ischemic heart disease and enzalutamide should be discontinued Grade 3-4 ischemic heart disease. Management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia should be optimized.

- **Falls and Fractures:** Across three randomized, placebo-controlled clinical studies, falls occurred in 10% of patients treated with enzalutamide compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 8% of patients treated with enzalutamide and in 3% of patients treated with placebo. Grade 3-4 fractures occurred in 2% of patients treated with enzalutamide and in < 1% of patients treated with placebo. The median time to onset of fracture was 337 days (range: 2 to 996 days) for patients treated with enzalutamide. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed

in the studies. Patients should be evaluated for fracture and fall risk. Patients who are at risk for fractures should be monitored and managed according to established treatment guidelines. Use of bone-targeted agents should be considered

- **Embryo-Fetal Toxicity:** The safety and efficacy of enzalutamide have not been established in females. Based on animal reproductive studies and mechanism of action, enzalutamide can cause fetal harm and loss of pregnancy when administered to a pregnant female. Males with female partners of reproductive potential should use effective contraception during treatment with enzalutamide and for 3 months after the last dose of enzalutamide. Enzalutamide should not be handled by females who are or may become pregnant.

9.4 Abiraterone

Abiraterone is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with mCRPC and for patients with metastatic high-risk castration-sensitive prostate cancer. See the most up to date version of the US abiraterone prescribing information for detailed information on this agent (www.zytigahcp.com).

9.4.1 Supplier

Commercial supplies of abiraterone will be used and charged to the patient and/or his insurance company.

9.4.2 Summary of Adverse Events Associated with Abiraterone

The most common adverse reactions (≥10%) reported in five randomized clinical trials that occurred more commonly (>2%) in the abiraterone arm were fatigue, joint swelling or discomfort, edema, hot flush, nausea, diarrhea, vomiting, upper respiratory infection, cough, hypertension, hypokalemia and headache. The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia and hypokalemia.

The following warnings are associated with the use of abiraterone (from the March 2018 prescribing information):

- **Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess:** Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17. In the four randomized clinical trials using prednisone 5mg twice daily in combination with 1000mg abiraterone daily, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with abiraterone. In the randomized clinical trial which used prednisone 5mg daily in combination with 1000mg abiraterone daily (castration-sensitive population), grade 3 to 4 hypertension occurred in 20% of patients, grade 3 to 4 hypokalemia in 10% of patients and grade 3 to 4 edema in 1% of patients in the abiraterone arm. Use caution when treating patients whose

underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use abiraterone with caution in patients with a history of cardiovascular disease. The safety of abiraterone in patients with LVEF < 50% or NYHA Class III to IV heart failure is not established.

- **Adrenocortical insufficiency:** Adrenal insufficiency occurred in the five randomized clinical studies in 0.3% of patients taking abiraterone and in 0.1% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone.

- **Hepatotoxicity:** In postmarketing experience, there have been abiraterone-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths. In the five randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 6% of patients who received abiraterone, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1.1% of patients taking abiraterone. No deaths clearly related to abiraterone were reported due to hepatotoxicity events in these clinical trials. The safety of abiraterone re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

9.4.3 Compliance

Patients will receive diaries that include the instructions for home administration of abiraterone and a log to record the date and time of each dose as well as the number and strength (mg) of tablets taken. Detailed instructions for completion and review of the diaries will be provided in the study manual.

The study center staff will check the patient's diary at the Day 1 visit of each new treatment cycle and at the End of Treatment Visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

9.5 Prednisone

Prednisone is a synthetic adrenoglucocorticoid. It is commercially available as a generic in tablet form for oral administration. It is indicated for a variety of medical conditions, including cancer.

9.5.1 Supplier

Commercial supplies of prednisone will be used and charged to the patient and/or his insurance company.

9.5.2 Summary of Adverse Events Associated with Prednisone

See Reference [76] for a more complete summary of AEs associated with glucocorticoids.

The side effects from systemic glucocorticoids are usually dose and duration dependent, and can impact virtually all body systems. Common side effects include thinning of the skin, purpura, Cushingoid appearance, weight gain, sleep disturbance and mood changes. Hyperglycemia is common if these agents are used in patients with pre-existing diabetes or those at risk of diabetes for other reasons. Cataracts are also common with prolonged (>1 year) of glucocorticoids. Other risks of concern with glucocorticoids include an increased risk of cardiovascular disease and hypertension (particularly when glucocorticoids are prescribed in patients with pre-existing cardiac or renal disease), increased risk of peptic ulcer disease and gastritis (especially when patients are also taking nonsteroidal anti-inflammatory agents), osteoporosis, increased fracture risk, osteonecrosis, myopathy, edema, and immunosuppression with an increased risk of infection. With the exception of cataracts and some of the cardiac and bone toxicities, adverse effects from glucocorticoids are at least partially reversible upon discontinuation. Also see Section 6.2.5 and reference [75].

10 DISEASE EVALUATION

10.1 PSA Evaluation

For the purpose of PSA evaluation, baseline PSA will be the PSA measured pre-dose on C1D1 (or the PSA measured during Screening if PSA was collected ≤ 7 days prior to C1D1).

10.1.1 PSA Progression (for Study Entry)

Phase 1b Dose Escalation:

If progressive disease at study entry is based on PSA, PSA increase must be ≥25% and an absolute increase of ≥2 ng/mL in < 6 months from end of last therapy prior to enrollment; **NOTE**: increase should be measured from nadir (in patients with a decline in PSA during last therapy) or baseline (in patients without a decline in PSA during last therapy.

Phase 1b HPEC(s) and Phase 2:

If progressive disease at study entry is based on PSA, PSA must be ≥ 2 ng/mL (or PSA ≥ 1 ng/mL if PSA progression is the only manifestation of progressive disease) and rising PSA must be documented by at least 2 consecutive measurements a minimum of 1-week apart.

10.1.2 PSA 50% Response

To be evaluable for PSA 50% response, baseline PSA must be ≥ 2 ng/mL (unless PSA progression is the only manifestation of progressive disease, in which case baseline PSA must be ≥ 1 ng/mL).

PSA response is defined according to the Prostate-Specific Antigen Working Group criteria [77].

PSA 50% response is defined as a ≥50% reduction in PSA from baseline. The reduction must be confirmed by a second PSA value 4 or more weeks later. PSA50 is the proportion of patients with a PSA 50% response.

10.1.3 PSA Progression (on Treatment)

PSA progression during study treatment is defined according to PCWG3.

Early rises (before 12 weeks) in PSA should be ignored.

For patients with PSA decline from baseline, the PSA progression date is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later.

For patients without a PSA decline from baseline, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented beyond 12 weeks.

10.2 PCWG3 Criteria (Radiographic Evaluation)

The PCWG3 criteria are based on modifications of the RECIST 1.1 criteria. See Section 10.3 below for details on RECIST 1.1.

10.2.1 Measurable and Nonmeasurable Disease

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable Lesions:
Visceral disease should be designated separately as lung, liver, adrenal, or central nervous system (CNS) and is considered measurable if an individual lesion is ≥ 1 cm in its longest dimension.

Nodal disease should be measured in the short axis and recorded by location: pelvic disease should be classified as locoregional, and extrapelvic disease (retroperitoneal, mediastinal, thoracic, or other) as metastatic. Nodes ≥ 1.5 cm in the short axis are considered pathologic and measurable.

Nonmeasurable Lesions:
All other lesions, including small lesions (longest diameter < 1 cm) and pathological lymph nodes with ≥ 1 to <1.5 cm short axis are considered non-measurable. Lesions that are considered non-measurable include bone lesions (only).

10.2.2 Target and Non-Target Lesions (Soft Tissue)

RECIST 1.1 criteria should be followed for selecting target and non-target lesions with the following caveats:

- Measurable and nonmeasurable lesions are defined per PCWG3 (see Section 10.2.1 above)
- Up to five target lesions per site of metastatic spread (e.g., lung, liver, lymph nodes as separate sites) should be recorded to address disease heterogeneity and to track patterns of metastatic progression

10.2.3 Objective Response (Soft Tissue)

Patients with measurable soft tissue disease at baseline will be followed for objective response (i.e., CR or PR).

A best overall response of CR and PR are defined per RECIST 1.1 with the following caveats:

- See Section 10.2.2 for information on target lesions.
- Record changes in nodal and visceral disease separately

- For visceral disease, record changes in liver, lung, adrenal, and CNS separately
- For nodal disease, record changes in pelvic (regional) nodes vs. extrapelvic (distant/metastatic) nodes separately

- Changes in tumor measurements indicative of a response must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

10.2.4 Objective Response (Excluding Parenchymal Lesions)

Patients with measurable disease in non-parenchymal soft tissue will be followed for objective response (excluding parenchymal lesions), which is defined as a CR or PR per PCWG3 in soft tissue excluding the parenchyma (i.e., liver and lung). Only non-parenchymal soft tissue will be considered, but otherwise the rules for objective response described in Section 10.2.3 will be followed.

10.2.5 Radiographic Progression

All patients will be followed for radiographic progression. **NOTE:** In the event that dosing with any of the agents is interrupted mid-cycle, the duration of cycle/treatment will not be extended (i.e., missed doses will not be made up). Therefore, the imaging assessments will remain on schedule. **NOTE**: for the HPEC(s) and for any phase 2 trial, sites will be required to submit all radiographic imaging for CRR. Details on the CRR will be provided in a CRR charter, provided as a document separate from the protocol.

A CT/MRI and bone scan should be done during Screening (baseline), every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) and at the End of Treatment Visit. For the crossover, CT/MRI and bone scan should be done prior to the first dose of CPI-1205 (unless completed ≤ 14 days prior to the start of CPI-1205), every 8 weeks (2 cycles) starting C3D1 for the first 24 weeks (6 cycles), and then every 12 weeks (3 cycles) and at the End of Treatment Visit. **NOTE:** CT/MRI and bone scan do not need to be repeated at the End of Treatment Visit if completed ≤ 28 days prior to the last dose of CPI-1205. Patients who discontinue study treatment for reasons other than radiographic progression (and who do not participate in the crossover if enrolled in the control arm of a randomized phase 2) and patients who discontinue study treatment for reasons other than radiographic progression after crossover will continue to have their disease evaluated as if patient had continued on treatment as per the respective Schedule of Eventsuntil another anti-cancer treatment is started, radiographic progression of disease (as determined by the investigator), death, loss to follow up or withdrawal of consent, whichever comes first.

In the table below, Week 9 refers to the first post-baseline scans, Week 17 to the second post-baseline scans, etc.

Patients are defined as having radiographic progression when they meet bone or soft tissue progression (at any site).

Radiographic progression of soft tissue lesions is defined per RECIST 1.1 with the following caveats:

- See Section 10.2.2 for information on target lesions
- Record changes in nodal and visceral disease (lung, liver, adrenal, and CNS) separately
- For visceral disease, clearly record type of progression (growth of existing lesions vs. development of new lesions) separately by site
- For nodal disease:
    - Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed
    - Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable
    - For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Table 10-1 PCWG3 Criteria for Radiographic Progression

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9	Bone lesions: 2 or more new lesions compared to **baseline** bone scan	Timing: at least 6 weeks after progression identified or at Week 17 visit.[b]	Two or more new bone lesions on bone scan (compared to Week 9 scan).
	Soft tissue lesions: Progressive disease on CT or MRI by modified RECIST 1.1[c]	Confirmation required for soft tissue disease (scan of same modality as demonstrated progression)[b]	Confirmation of progressive soft tissue disease by modified RECIST 1.1[c]
Week 17	Bone lesions: Two or more new lesions on bone scan compared to Week 9 bone scan.	Timing: at least 6 weeks after progression identified or at Week 25 visit. Required for bone lesions observed on bone scan.[b]	Persistent[d] or increase in number of bone lesions on bone scan compared to Week 17 scan.
	Soft tissue lesions: Progressive disease on CT or MRI by modified RECIST 1.1[c]	No confirmatory scan required for soft tissue disease progression.	n/a
Week 25 or	Bone lesions: Two or more new lesions compared to Week 9 bone scan.	Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan.[b]	Persistent[d] or increase in number of lesions on bone scan compared to prior scan.

later[e]	Soft tissue lesions: Progressive disease on CT or MRI by modified RECIST 1.1[c]	No confirmatory scan required for soft tissue disease.	n/a

[a] Progression detected by bone scan at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by CT/MRI at an unscheduled visit prior to Week 13 will require a confirmatory scan at least 6 weeks later whereas progression on or after Week 13 does not require confirmation.

[b] Confirmation must occur at the next available scan.

[c] Modifications to RECIST 1.1 for evaluation of soft tissue lesions are outlined above the table

[d] For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).

n/a, not applicable.

10.3 RECIST 1.1 Criteria

10.3.1 Measurable and Nonmeasurable Disease

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable Lesions:
Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Lesions:
All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target

lesions. See RECIST1.1 reference for details on tumors in previously irradiated fields and bone lesions with soft tissue components.

10.3.2 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

10.3.3 Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.3.4 Evaluation of Target Lesions

NOTE: In addition to the information below, also see Section 4.3.2 in the international criteria proposed by the RECIST Committee, version 1.1 [74] for special notes on the assessment of target lesions.

Table 10-2 Evaluation of Target Lesions (RECIST 1.1)

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 of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

10.3.5 Evaluation of Non-Target Lesions

Table 10-3 Evaluation of Non-Target Lesions (RECIST 1.1)

CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the Sponsor-Investigator.

10.3.6 Evaluation of Best Overall Response

Table 10-4 Evaluation of Best Overall Response (RECIST 1.1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE

PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = inevaluable			

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

10.4 Unequivocal Clinical Progression

Unequivocal clinical progression includes development of any of the following clinically significant disease-specific events:

- Spinal cord or nerve root compression
- Pathologic fracture
- Metastatic disease in an anatomy for which no baseline scan (e.g., spine, base of skull) is available for comparison to allow documentation of interval change on serial imaging studies.
- Progressive disease in an anatomy for which there is a baseline imaging assessment but serial imaging has not been performed (e.g., prostate bed)
- A clinical indication for radiation therapy
- At least 2 of the following clinical signs/symptoms in comparison to baseline:
    - An increase in ECOG performance status of > 1 grade
    - ≥ 10% weight loss, not attributable to intentional weight loss
    - New urinary outflow obstruction attributable to cancer. Urinary retention may be due to disease progression, treatment induced prostatitis, or stricture from scar tissue after surgery, so subjects should be carefully evaluated.

- Progressive anemia, defined as either:
  - a decrease in hemoglobin of ≥ 2 g/dL and to a level below the lower limit of normal in the central lab reference range, **or**
  - a requirement for therapy with a hematopoietic growth factor (e.g., Procrit®) or transfusion with packed red blood cells for anemia

10.5 Enumeration of CTCs

Blood will be collected for the enumeration of CTCs following recommendations from PCWG3. Favorable or unfavorable status will be determined.

Unfavorable is defined as five or more cells per 7.5 mL of blood.

Favorable is defined as four or fewer cells per 7.5 mL of blood.

CTC 30% response is defined as ≥ 30% reduction in CTCs from baseline in patients with unfavorable CTC status. Any CTC 30% response must be confirmed by an additional CTC enumeration at least 4 weeks later.

CTC conversion (i.e., conversion from unfavorable to favorable) is another way to measure response via CTCs. **NOTE:** Any conversion from unfavorable to favorable CTC status must be confirmed by an additional CTC enumeration at least 4 weeks later.

10.6 Skeletal Events (SREs and SSEs)

SREs are defined as: asymptomatic nonclinical fractures as evaluated via serial imaging, clinical pathologic fractures, spinal cord compression, and surgery or radiation therapy to bone.

SSEs are defined as: symptomatic fracture, radiation or surgery to bone, or spinal cord compression.

10.7 Pain/Analgesic Usage

[redacted]

Pain Progression:
Pain progression will be evaluated in all patients.

For patients with no baseline pain, pain progression is defined as the development of pain. For patients with baseline pain, progression is defined as a ≥2-point increase in pain on the NRS on 2 consecutive evaluations 4 weeks apart, without any decrease in analgesic usage score.

Opioid Usage:
Opioid usage is defined as a 2 or 3 on the WHO analgesic ladder.

11 STATISTICAL AND QUANTITATIVE ANALYSES

11.1 General Considerations and Missing Data Handling

Unless otherwise specified, categorical variables will be presented as frequencies and percentages, and continuous variables will be presented with the number of non-missing values, mean, standard deviation, median, minimum and maximum values. Graphs may also be presented where appropriate. Unscheduled visits will not be included in by-visit summaries, but will be considered in baseline derivations and in analyses such as maximum grade shift from baseline.

In general, missing data will not be imputed unless otherwise specified. For the derivation of treatment-emergent adverse events or concomitant medications, however, the missing or partial date will be temporarily imputed for programming purposes. The details will be further specified in the statistical analysis plan (SAP).

11.2 Statistical Methods

[redacted]

11.2.2 Randomization and Stratification

There will be no randomization in phase 1b (dose escalation or HPEC[s]) or in the phase 2 single arm trial (if conducted). The variability in the dose of CPI-1205 with which patients will be treated during phase 1b dose escalation, and the small size of this study preclude the use of any meaningful stratification in phase 1b (all cohorts) or in the phase 2 single arm trial.

If phase 2 is pursued, at least one randomized phase 2 trial is planned. For the randomized phase 2 study(ies), eligible patients will be randomly assigned in a 1:1 ratio to the combination arm (CPI-1205 [with or without cobicistat] at the RP2D in combination with enzalutamide or abiraterone/prednisone) or the control arm (enzalutamide or abiraterone/prednisone as monotherapy). [redacted]

At least 50% of patients in any phase 2 trial opened will have measurable soft tissue disease.

11.2.3 Populations for Analysis

There are 5 patient populations for the purpose of statistical analysis in this study.

11.2.3.1 Population Evaluable for Safety

The population of patients evaluable for safety is defined as all patients who receive any amount of study treatment.

11.2.3.2 Population Evaluable for DLT

During phase 1b dose escalation, patients are evaluable for DLT if, in Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the combination), is observed for ≥ 28 days following the first dose, and is considered by the SSC to have sufficient safety data available to conclude that a DLT did not occur. Patients who do not meet these minimum treatment and safety evaluation requirements and who do not experience DLT will be replaced with new patients if the minimum evaluable patients per dose level has not been satisfied. **NOTE**: If a patient misses >25% of doses in Cycle 1 for reasons not related to toxicity, the patient can be replaced. If a patient misses >25% of doses in Cycle 1 for reasons related to toxicity, this will be considered a DLT (see Section 5.4.6), and the patient cannot be replaced. Patients will be analyzed by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

11.2.3.3 Populations Evaluable for Pharmacokinetics

The population of patients evaluable for the PK of each of the drugs (CPI-1205, cobicistat, abiraterone and enzalutamide) is defined as all patients for whom there are sufficient dosing and concentration-time data for each drug to reliably estimate each drug's PK. These populations will be used for analyses of PK parameters.

[redacted]

11.2.3.5 Population Evaluable for Efficacy

Evaluation of the efficacy of the combinations will be assessed in all patients, when possible, during phase 1b dose escalation, in the phase 1b HPEC(s) and during phase 2.

A patient from a phase 1b HPEC is evaluable for the primary endpoint of objective response if:

- In Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the regimen)
- He has at least one post-baseline imaging assessment

Patients who are not evaluable for objective response will be replaced.

NOTE: all patients enrolled in a HPEC must have at least one measurable lymph node at study entry.

Any randomized phase 2 trial will be analyzed based on a modified intent-to-treat (mITT) population, which is defined as all randomized patients with at least 1 dose of study treatment and with at least one efficacy assessment. Patients who do not meet the criteria for being in the mITT population will be replaced.

If a single arm phase 2 trial is conducted, a patient is evaluable for the primary endpoints if:

- In Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the combination selected for phase 2)
- He has at least one post-baseline PSA measurement (if evaluable for PSA 50% response)
- He has at least one post-baseline CTC assessment (for patients with ≥ 5 CTCs)

- He has at least one post-baseline imaging assessment (for patients with measurable disease)

Patients who are not evaluable for the primary endpoints will be replaced. **NOTE:** baseline PSA will be the PSA measured pre-dose on C1D1 (or the PSA measured during Screening if PSA was collected ≤ 7 days prior to C1D1).

NOTE: At least 50% of patients of any phase 2 trial opened must have measurable soft tissue disease at study entry.

11.2.4 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be descriptively evaluated in phase 1b (all cohorts) and in the phase 2 single arm trial (if conducted). Demographic and baseline characteristics will be summarized by treatment arm for any randomized phase 2 trial. Data to be evaluated will include age, sex, race, and baseline characteristics.

11.2.5 MTD and RP2D determination

The MTD during phase 1b dose escalation will be determined for both CPI-1205/cobicistat + enzalutamide and CPI-1205/cobicistat + abiraterone/prednisone (and possibly for CPI-1205 without cobicistat). Patients will be assigned to dose levels in cohorts following the rules outlined in Section 5.4.3. [redacted] The MTD will not be determined until all patients entered into the cohort under evaluation have either completed Cycle 1 or experienced a DLT. The RP2D for each combination will be selected based on PK and overall tolerability data (i.e., DLT, cumulative and/or delayed toxicity that limits dosing) from all patients treated at different dose levels in this study and will not exceed the MTD. Only one of the CPI dosing schedules will be selected as the RP2D for each combination (i.e., with enzalutamide and with abiraterone/prednisone).

11.2.6 Efficacy Analysis

Efficacy results will be reported separately for phase 1b dose escalation, phase 1b HPEC(s) and phase 2. Within each phase, efficacy results will be reported by combination (within each schedule) and by dose cohort. If appropriate, results may also be reported across dose cohorts and/or phases for each combination.

For the phase 1b HPEC(s), ORR as determined by CRR will be estimated and reported along with an exact 95% confidence interval. The population evaluable for the primary endpoint will be used for this analysis. [redacted]

For the analysis of the composite response rates, and PSA50, ORR, and CTC 30% response rate in phase 2, if the trial is randomized between 2 treatment arms, treatment difference in these

proportions will be presented along with a 2-sided 95% Clopper-Pearson confidence interval and the estimated rates for each treatment will be reported with a 2-sided 95% Clopper-Pearson confidence interval. If a single arm phase 2 trial is conducted, the 2-sided 95% confidence interval will be presented for the estimated rates. If data allow, subgroup analyses may be considered for disease characteristics, or/and stratification factors.

More details on the efficacy analyses of other endpoints will be specified in the SAP.

[redacted]

11.2.8 Pharmacokinetics

Descriptive statistics will be used to summarize PK parameters for phase 1b dose escalation, phase 1b HPEC(s) and phase 2. PK parameters will be reported for each combination (within each schedule) and for each dose level. If appropriate, results may also be reported across dose cohorts and/or phases for each combination. PK parameters for each drug will include (but may not be limited to) C_{max}, T_{max}, AUC_{last}, C_{trough}, peak to trough ratio and accumulation ratio. [redacted] The population evaluable for PK will be used for these analyses.

[redacted]

11.2.10 Safety Analysis

The incidence of DLT will be tabulated for each combination and for each dose level during phase 1b dose escalation and for each phase 1b HPEC. In addition, to assess the relationship between toxicities and CPI-1205 dose, the preferred term of individual toxicities will be

summarized by their frequency and intensity for each dose level within each combination. Events that would qualify as a DLT, but that occur after 28 days will also be tabulated.

Safety will also be evaluated by the incidence of treatment-emergent AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the population evaluable for safety. Exposure to CPI-1205 (with and without cobicistat) and reasons for discontinuation will be tabulated.

Treatment-emergent AEs will be tabulated where treatment emergent is defined as any AE that occurs after administration of the first dose of study treatment and through 30 days after the last dose of study medication, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class, high level terms, and preferred terms and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Treatment-emergent AEs resulting in CPI-1205 discontinuation
- SAEs

The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥10% of all patients) will be tabulated by high level term and preferred term.

Descriptive statistics for the actual values of clinical laboratory parameters and change from baseline in clinical laboratory parameters will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values and the changes from baseline of vital signs and weight over time will be tabulated by scheduled time point.

All concomitant medications collected from Screening through the study period will be classified to preferred terms according to the WHO drug dictionary.

Additional safety analyses may be determined in order to most clearly enumerate rates of toxicities and to further define the safety profiles of the combinations.

[redacted]

[redacted]

12 ADVERSE EVENTS

12.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of the drug.

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention, dose hold, dose reduction or schedule change. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the laboratory section of the clinical study report.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

12.2 Evaluation of Adverse Events

The Investigator will determine the seriousness and severity (intensity) of each AE, and relationship of each AE to the use of each study drug based on the definitions described below. The relationship to CPI-1205, abiraterone, enzalutamide and prednisone will assessed separately.

12.2.1 Serious Adverse Event

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires in patient **hospitalization or prolongation of existing hospitalization***.
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and

may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 patient hospitalization, or the development of drug dependency or drug abuse.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. However, the investigator must determine severity (intensity) of all AEs (whether serious or not) as outlined in Section 12.2.2.

12.2.2 Severity of AEs

For both SAEs and non-serious AEs, the investigator must determine the severity (intensity) of the event. Intensity for each AE, including any laboratory abnormality, will be determined by the investigator using the NCI CTCAE, Version 4.03, as a guideline, wherever possible. The criteria are provided in the study manual and also are available online at http://ctep.cancer.gov/reporting/ctc.html. In those cases where the NCI CTCAE criteria do not apply, intensity should be defined according to the following criteria:

Table 12-1 Severity Criteria

Mild	Awareness of sign or symptom but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities
Life Threatening	Immediate risk of death from the reaction as it occurred
Death	Death related to adverse event

12.2.3 Relationship to Study Drug

For both SAEs and non-serious AEs, the investigator must determine the relationship of the event to each study drug.

The causal relationship to study treatment will be determined by the investigator according to best medical judgment, as follows:

- Definitely related: This category applies when, after careful medical consideration, there is almost no consideration of other causation.
- Probably related: There is a clinically plausible time sequence between onset of the AE and study treatment administration. The AE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study drug(s).
- Possibly related: There is a clinically plausible time sequence between onset of the AE and study treatment administration, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding study drug withdrawal may be lacking or unclear. “Possible” should be used when study treatment administration is one of several biologically plausible causes of the AE.
- Unlikely related: The AE is most likely due to a non-study-treatment-related cause. However, association with the study treatment cannot be completely ruled out.
- Unrelated: Another cause of the AE is most plausible and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study treatment administration and/or a causal relationship is considered biologically implausible.

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

12.2.4 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which it is at least possible that the drug is the cause (see Section 12.2.3). A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug (see Section 12.2.5).

12.2.5 Adverse Reaction

An adverse reaction means any adverse event caused by a drug (i.e., definitely related). Adverse reactions are a subset of all SARs where there is reason to conclude that the drug caused the event.

12.2.6 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.2.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an event that meets the criteria for an SAE (see Section 12.2.1), that is at least possibly related to study drug (see Section 12.2.3) and is unexpected (see Section 12.2.6).

12.3 Monitoring of Adverse Events and Period of Observation

Monitoring of AEs and SAEs will be conducted throughout the study. All AEs, both serious and non-serious, and deaths will be recorded on the eCRF from the time of informed consent until 30 days after administration of the last dose of study drug(s). All AEs considered at least possibly related to study treatment (see Section 12.2.3) and all SAEs that occur during the reporting period will continue to be followed until the event resolves, the investigator assesses the event as stable, the event is determined to be irreversible, or the patient is lost to follow-up.

Any SAE that occurs at any time after completion of the study and the designated 30 day follow-up period, which the investigator considers to be related to CPI-1205, must be reported to the study CRO (see Section 12.5).

12.4 Procedures for Recording Adverse Events and SAEs

All AEs, both serious and non-serious, and deaths will be recorded on the eCRF from the time of informed consent until 30 days after administration of the last dose of study drug(s). All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded in the appropriate section of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE and must be recorded in the appropriate sections of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

12.5 Procedures for Reporting SAEs to Sponsor

All SAEs that occur during the course of the study, as defined in Section 12.2.1, must be reported by the study site to the study CRO, following instructions provided in the Study Manual, within 24 hours from the point in time when the site becomes aware of the SAE. In addition, all SAEs, including all deaths that occur through 30 days after administration of the last dose of CPI-1205 must be reported to the study CRO within 24 hours of the site's knowledge of the event.

All SAEs and deaths must be reported whether or not considered causally related to treatment. The information collected will include a minimum of the following: patient identification number, a narrative description of the event, and an assessment by the investigator as to the intensity (severity) of the event (see Section 12.2.2) and relatedness to drug(s) (see Section 12.2.3). A sample of the SAE Form may be found in the study regulatory binder. Follow-up information on the SAE may be requested by Constellation or the study CRO.

Table 12-2 SAE Reporting Contact Information

CRO Pharmacovigilance
Email: [redacted]
Fax Number: [redacted]

12.6 Reporting to Regulatory Authorities and Study Sites

In accordance with local guidelines, Constellation or its designee will notify, in an expedited manner, the appropriate competent authorities (including the FDA), applicable IRBs, and investigators of SUSARs associated with the use of CPI-1205.

12.7 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a patient's partner becomes pregnant or suspects she is pregnant while her partner is participating in this study, the treating physician must be informed immediately. The study CRO must also be contacted immediately by faxing a completed Pregnancy Form, in accordance with the instructions provided in the Study Manual. The pregnancy must be followed through the final pregnancy outcome one month after the expected due date.

12.8 Definition and Procedures for Reporting Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual patient enrolled in the trial. Even if it does not meet other criteria for a serious adverse event (SAE), any overdose must be recorded in the trial medication section of the eCRF and reported in an expedited manner following the procedure outlined below.

If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment should be instituted immediately.

In the event of an overdose of any study treatment, the investigator and Sponsor should be immediately notified. The study CRO must also be contacted immediately by faxing a completed Overdose Form, in accordance with the instructions provided in the Study Manual. The patient should be carefully monitored for potential AEs and symptomatic treatment instituted as per institutional standards of care. Continued study treatment may be decided upon by the investigator in consultation with the Sponsor.

13 ADMINISTRATIVE REQUIREMENTS

13.1 Good Clinical Practice

The study will be conducted in accordance with International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 Data Quality Assurance

Constellation or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect trial site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. Constellation will have read-only access to all data upon entry in the EDC application.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

13.3 Electronic Case Report Form Completion

Constellation will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for which they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, other observations, and patient status.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. An explanation should be provided for all missing data.

The audit trail entry will show the user's identification information, and the date and time of the correction. The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he is responsible.

Constellation will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc (CD) or other electronic media will be placed in the investigator's study file.

13.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Constellation will be followed, in order to comply with GCP guidelines. On-site and remote review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Constellation or its designee. Monitoring will be done by personal visits from a representative of the sponsor or designee (site monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, e-mail, and fax).

13.5 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and wellbeing of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, IB, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator or the sponsor, as allowable by local regulations.

13.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s) and will be subject to approval by Constellation or its designee.

13.7 Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports and communications will identify the patient by initials where permitted and/or by the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Constellation or its

designee and regulatory authority(ies) access to the patient's original medical records for verification of data collected on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained in accordance with all applicable laws and regulations.

13.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Constellation, and given approval by the IEC/IRB and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the investigator and Constellation. Changes to the protocol will require written IEC/IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. If applicable regulatory authority(ies) permit, the IEC/IRB may provide expedited review and approval for minor change(s) in ongoing trials that have the approval of the IEC/IRB. Constellation will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact Constellation, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the eCRF and source documentation.

13.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Constellation's quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

13.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol.

Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Constellation (or disposal of the drug, if approved by Constellation) will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Constellation. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

All non-dispensed, and dispensed but unused, study drug will be retained at the site until it is inventoried by the monitor. All non-dispensed, dispensed but unused, or expired study drug will be returned to Constellation or if authorized, disposed of at the study site and documented. All

material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

13.11 Closure of the Study

Study participation by individual sites or the entire study may be prematurely terminated, if in the opinion of the investigator or Constellation, there is sufficient reasonable cause.

Written notification documenting the reason for study termination will be provided to the investigator or Constellation by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or non-evaluable data
- Plans to modify, suspend, or discontinue the development of the study drug

Should the study be closed prematurely, all study materials (study medication, etc.) must be returned to Constellation. The site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded.

Within 15 days of premature closure, Constellation must notify the FDA and IEC/IRBs, providing the reasons for study closure.

13.12 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and communicate this information to Constellation or its designee.

14 USE OF INFORMATION

All information regarding CPI-1205 supplied by Constellation to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Constellation. It is understood that there is an obligation to provide Constellation with complete data obtained during the study. The information obtained from the clinical trial will be used towards the development of CPI-1205 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical trial and evaluation of results by Constellation, hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group, comprising Constellation employees and study investigators, will be formed to oversee the publication of the study results that will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with Constellation.

A prepublication manuscript or abstract is to be provided to Constellation a minimum of 30 days prior to the intended submission date of the manuscript or abstract to a publisher.

Within 30 days after receipt by Constellation of the notification, Constellation shall inform the investigational sites whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Constellation's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Constellation's request.

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16 APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Reference: Oken MM, Creech RH, Hormey RH et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.	

APPENDIX 2: COCKCROFT-GAULT EQUATION

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

APPENDIX 3: NYHA CLASSIFICATION

Class	Description
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.
Excerpt from Oxford Textbook of Medicine. Vol. 2, p.2228. Oxford Press. 1997.