Protocol I3Y-MC-JPEG (e)

CYCLONE 3: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination With Abiraterone Plus Prednisone in Men With High-Risk Metastatic Hormone-Sensitive Prostate Cancer

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Title Page

Protocol Title:

CYCLONE 3: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination with Abiraterone plus Prednisone in Men with High-Risk Metastatic Hormone-Sensitive Prostate Cancer

Protocol Number: I3Y-MC-JPEG

Amendment Number: e

Compound: Abemaciclib (LY2835219)

Brief Title:

CYCLONE 3: A Study of Abemaciclib with Abiraterone in Men with High-Risk Metastatic Hormone-Sensitive Prostate Cancer

Study Phase: Phase 3

Acronym: CYCLONE 3

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 139694

EU trial number: 2022-500461-28-06

Document ID: VV-CLIN-117592

Approval Date: Protocol Amendment (e) Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (d)	*18-Jul-2023*
Amendment (c)	*20-Oct-2022*
Amendment (b)	*05-Aug-2022*
Amendment (a)	*25-Mar-2022*
Original Protocol	*01-Feb-2022*

Amendment [e]

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment:

The purpose of this amendment is to clarify the drug distribution timing during the continued-access period of this study.

Section # and Name	Description of Change	Brief Rationale
1.3.2 Continued Access SoA	Added footnote clarifying how often investigational products may be dispensed during continued access period.	Clarification
	Administer abemaciclib – Addition to Instructions to say "Abemaciclib can be administered every 28 ± 3, 56 ± 3, or 84 ± 3 days at investigator discretion. Up to 3 cycles of abemaciclib dosage may be dispensed at a time."	Clarification
	Administer abiraterone – Addition to Instructions to say "Abiraterone supplied by sponsor can be administered every 28 ± 3, 56 ± 3, or 84 ± 3 days at investigator discretion. In cases of site sourced abiraterone, frequency of dispensing is left to the judgment of the investigator based on standard of care"	Clarification
	Administer prednisone – Addition to Instructions to say "Prednisone supplied by sponsor can be administered every 28 ± 3, 56 ± 3, or 84 ± 3 days at investigator discretion. In cases of site sourced prednisone, frequency of dispensing is left to the judgment of the investigator based on standard of care."	Clarification

Section # and Name	Description of Change	Brief Rationale
6.6 Continued Access to the Study Intervention after the End of the Study	Added 6 bullets defining when participants will be discontinued from study intervention. Removed 1st sentence in 4th paragraph regarding ending of participant's continued-access period.	Clarification

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

CYCLONE 3: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination with Abiraterone plus Prednisone in Men with High-Risk Metastatic Hormone-Sensitive Prostate Cancer

Brief Title:

CYCLONE 3: A Study of Abemaciclib with Abiraterone in Men with High-Risk Metastatic Hormone-Sensitive Prostate Cancer

Regulatory Agency Identifier Number(s):

IND: 139694

EU trial number: 2022-500461-28-06

Rationale:

Prostate cancer is a leading cause of mortality and morbidity globally and represents a substantial public health burden. With nearly 1.4 million new cases and 375,000 deaths worldwide, prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men in 2020 (Sung et al. 2021).

Men with mHSPC have either primary progressive disease or present with metastases at initial diagnosis (de novo mHSPC). While ADT alone or in combination with first-generation anti-androgens has been the mainstay of treatment for mHSPC, the treatment landscape has changed radically in recent years. Life-prolonging treatments now include docetaxel chemotherapy and novel hormonal agents, such as abiraterone, apalutamide, and enzalutamide. Despite these significant recent improvements, there is still a pressing medical need for tailored treatment approaches, particularly for patients with high-risk disease who experience shorter survival outcomes with current approved treatments. For these high-risk patients, early treatment intensification with novel combination therapy has the potential to meaningfully improve clinical outcomes.

Abemaciclib is a potent and selective oral inhibitor of CDK4 & 6 that is approved for the treatment of early and advanced/metastatic HR+/HER2- breast cancer (Verzenio package insert, 2021). CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine whether adding abemaciclib to abiraterone plus prednisone[a] improves radiographic progression-free survival (rPFS).	• rPFS assessed by the investigator.
Secondary	
• To evaluate improvements in other clinically relevant efficacy endpoints with the addition of abemaciclib to abiraterone plus prednisone.	• rPFS by blinded, independent, central review (BICR) • Clinical PFS (cPFS) • Castration-resistant prostate cancer (CRPC)-free survival • Time to symptomatic progression • Time to PSA progression • Time to initiation of new anticancer therapy • Overall survival (OS).
• To characterize the safety of adding abemaciclib to abiraterone plus prednisone.	• The safety endpoints evaluated will include, but are not limited to, the following: AEs, TEAEs, SAEs, clinical laboratory tests, ECGs, vital signs, and physical examinations.
• To characterize the PK of abemaciclib when administered in combination with abiraterone.	• Concentrations of abemaciclib.
• To assess patient-reported pain and HRQoL.	• Time to pain progression • Time to deterioration in HRQoL measured by the FACT-P (Physical Well-Being and PCS scores) and EQ-5D-5L.

Abbreviations: AE = adverse event; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life – 5 dimensions – 5 level; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL - health-related quality of life; PK = pharmacokinetics; PSA = prostate-specific antigen; PCS = physical component summary; rPFS = radiographic progression-free survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Prednisone implies prednisone or prednisolone.

Overall Design:

CYCLONE 3 is a multinational, randomized, double-blind, placebo-controlled, Phase 3 study to assess the safety and efficacy of adding abemaciclib to abiraterone plus prednisone in patients with high-risk mHSPC. High-risk is defined as the presence of ≥4 bone metastases and/or ≥1 visceral metastases.

Participants will be randomized in a 1:1 ratio to receive abiraterone plus prednisone and abemaciclib (experimental arm) or matching placebo (control arm). Randomization will be stratified according to the following factors:

- de novo metastatic prostate cancer (metastatic disease at initial diagnosis) (Yes vs. No).
- visceral metastases (Yes vs. No).

A diagram of the study design is provided below in Section 1.2.

Brief Summary:

This Phase 3, randomized, double-blind, placebo-controlled study is designed to assess the safety and efficacy of abemaciclib in combination with abiraterone plus prednisone for the treatment of patients with high-risk metastatic hormone-sensitive prostate cancer (mHSPC). The primary objective is to determine whether abemaciclib, an oral selective inhibitor of CDK4 & 6, added to standard androgen deprivation therapy and abiraterone plus prednisone delays radiographic disease progression.

Study Population:

This study will enroll participants with prostate cancer that has spread to other parts of the body and still responds to treatments to lower testosterone, a condition referred to as metastatic hormone-sensitive prostate cancer (mHSPC). In addition, participants must have at least 1 of the 2 following high-risk features:

- Disease that has spread to the bones with evidence of 4 or more lesions.
- Disease that has spread to the viscera, which are the soft internal organs of the body (for example, the lungs, liver, and the organs of the digestive system).

Participants should not have previously received systemic treatment for metastatic prostate cancer except for up to 3 months of ADT (LHRH agonist/antagonist or bilateral orchiectomy), with or without first-generation anti-androgen, prior to randomization.

Participants who have not undergone bilateral orchiectomy are required to continue background ADT with an LHRH agonist/antagonist throughout the study.

Medical conditions, including but not limited to, inflammation and scarring of the lungs, severe shortness of breath, cardiac arrhythmia, heart disease, uncontrolled hypertension, chronic liver disease, adrenal dysfunction, or active systemic infections may preclude participation in the study.

The complete list of eligibility criteria is provided in the Section 5 of this protocol.

Number of Participants:

Approximately 900 participants will be randomized.

Treatment Arms and Duration:

Abiraterone and prednisone (or prednisolone):

All participants will receive therapy with abiraterone CCI once daily plus prednisone CCI
Prednisolone may be used in lieu of prednisone per local abiraterone prescribing information or where prednisone is not commercially available; therefore, hereafter in this protocol prednisone implies prednisone or prednisolone.

Blinded study drug:

- Experimental arm: Abemaciclib CCI orally CCI (see Section 4.3).
- Control arm: Placebo CCI orally CCI

Note: Participants who have not undergone bilateral orchiectomy are required to continue background ADT with an LHRH agonist/antagonist throughout the study.

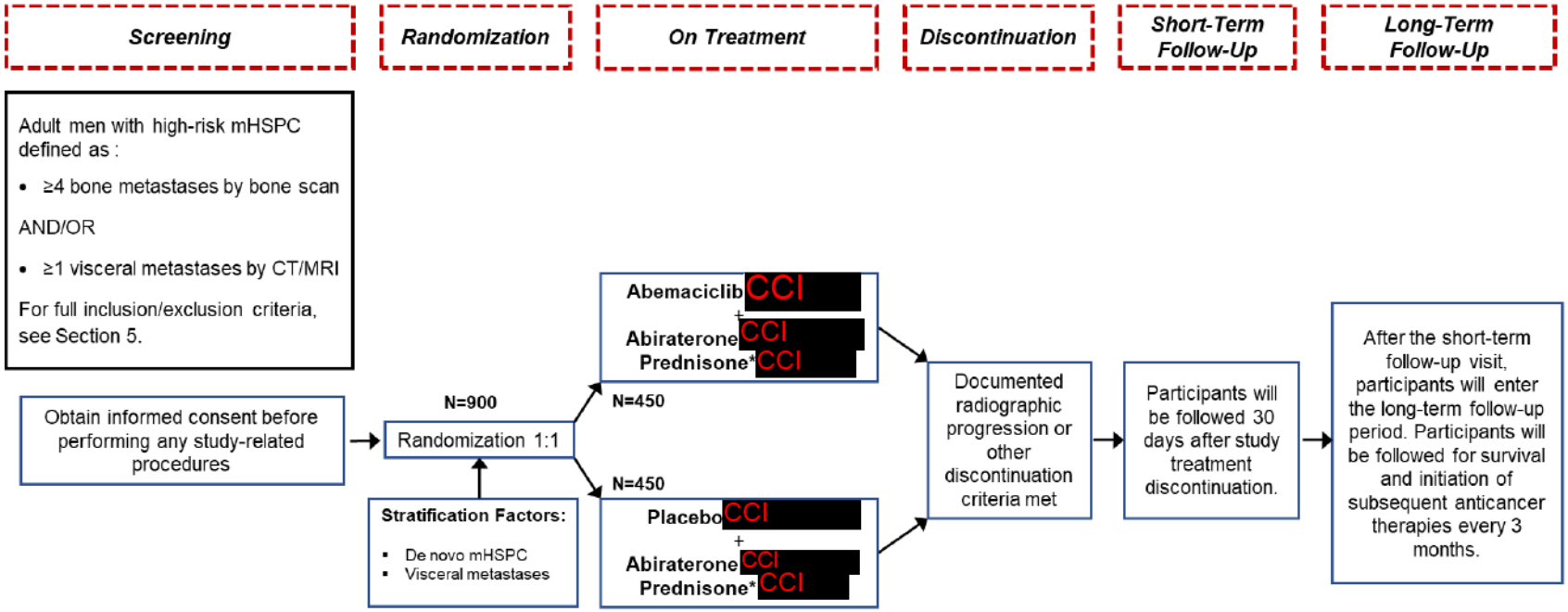
The study includes a screening period of up to 28 days prior randomization to establish eligibility. Abiraterone plus prednisone and abemaciclib/placebo will be initiated ≤7 days following randomization, administered in 28-day treatment cycles, and continued until radiographic progression, unacceptable toxicity, or until other discontinuation criteria are met (see Section 7.1). All participants discontinuing study treatment will enter the short- and long-term follow-up periods and have procedures performed as shown in the SoA (Section 1.3), except those lost to follow-up, those who withdraw informed consent or death.

Ethical Considerations of Benefit/Risk:

The potential risks of abemaciclib in combination with abiraterone plus prednisone are justified in consideration of the measures to minimize these risks and the anticipated benefit of improved disease control, as measured by radiographic progression-free survival in participants with high-risk metastatic hormone-sensitive prostate cancer. For these high-risk patients, this novel combination therapy has the potential to meaningfully improve clinical outcomes.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: CCI CT = computed tomography; LHRH = luteinizing hormone-releasing hormone; mHSPC = metastatic hormone-sensitive prostate cancer; MRI = magnetic resonance imaging; N = number of participants; QD = once daily.

* Prednisolone may be used in lieu of prednisone per local abiraterone prescribing information or where prednisone is not commercially available.

Participants who have not undergone bilateral orchiectomy are required to continue background androgen deprivation therapy with an LHRH agonist/antagonist throughout the study.

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks (see Section 6.6, Continued Access).

1.3. Schedule of Activities (SoA)

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		Every Cycle Day 1	Cycle 1 & Cycle 2 Day 15	Cycle 3 Day 15	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
General								
Informed consent	X							Written informed consent must be obtained within 28 days prior to randomization AND prior to conducting any protocol-specific tests/procedures.
Inclusion / exclusion criteria	X							Review and confirm inclusion and exclusion criteria prior to randomization.
Demographics	X							Include race, ethnicity, gender, and birth date per local regulations.
Preexisting conditions and medical history	X							Including assessment of preexisting conditions, historical illnesses that resolved, relevant surgical history and habits (such as tobacco and alcohol use).
Prior treatments for prostate cancer	X							Record all prior anticancer therapy for prostate cancer (for example, systemic therapy, surgery, radiopharmaceuticals, and radiotherapy).
Prior and concomitant medication	Continuous from time of Informed Consent Form signature until 30 days after the last dose of study treatment.							Collect concomitant medications at screening and throughout the study including short-term follow-up. Includes over-the-counter prescriptions and analgesics use.
Physical examination		X	X			X		- Complete physical examination with height, weight, and vital signs (temperature, blood pressure, pulse rate, pulse oximetry) will be performed at screening. - Symptom-directed physical examination, measurement of weight, and vital signs will be performed during clinic visits at the start of each cycle and V801. Does not need to be repeated on C1D1 if assessed ≤7 days at screening, unless clinically indicated. - Additional examinations should be performed as clinically indicated.

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		Every Cycle Day 1	Cycle 1 & Cycle 2 Day 15	Cycle 3 Day 15	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
ECOG PS		X	X			X		Does not need to be repeated on Cycle 1 Day 1 if assessed at screening ≤7 days.
Remote Telehealth Visit			Every other cycle starting on Cycle 14 (Cycles 14, 16, 18, etc.)			X		- Starting at Cycle 14, if deemed appropriate by the investigator, participants may have remote telehealth (telemedicine/telephone) visits every other cycle (Cycles 14, 16, 18, etc.). Laboratory assessments and other clinic procedures (for example, physical examination, vitals, and PROs) are not required on cycles when remote telehealth visits are performed. During telehealth visits, ALT, AST and bilirubin monitoring may be performed locally per investigator discretion in accordance with the abiraterone prescribing information. If clinically indicated or at any time, participants can return to the standard clinic visit schedule (in-person clinic visits on Day 1 of each cycle). - Detection of new or worsening AEs, change in concomitant medications, and symptoms suspicious of disease progression are highly important. The investigator or another medically qualified individual is expected to conduct a comprehensive and systematic assessment of these symptoms during the remote visit. - Unscheduled clinic visits and any corresponding procedures deemed necessary are at the discretion of the investigator. Unscheduled visits may include physical examinations, vital signs, ECOG performance status, tumor and/or symptomatic progression assessment(s), central chemistry and hematology, return of study intervention, or resumed dosing, if previously interrupted. - Participants who experience ≥ Grade 3 laboratory abnormality considered possibly related and clinically significant by the investigator, at any time during the on-treatment period, will continue to have in-person clinic visits with study procedures as outlined in the SoA.

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		**Every Cycle** **Day 1**	**Cycle 1 & Cycle 2** **Day 15**	**Cycle 3** **Day 15**	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
Laboratory Assessments								
Coagulation		**X**				**X**		- See Section 10.2. Repeat if clinically indicated.
Urinalysis		**X**				**X**		- See Section 10.2. Repeat if clinically indicated.
PSA		**X**	**X**			**X**		- See Section 10.2. Repeat if clinically indicated. - PSA, testosterone, hematology, and clinical chemistry do not need to be repeated on Cycle 1 Day 1 if assessed ≤7 days at screening unless clinically indicated. - Refer to Section 8.2.2 for more frequent hepatic monitoring.
Testosterone		**X**	**X**			**X**		
Hematology		**X**	**X**	**X**		**X**		
Clinical chemistry		**X**	**X**	**X**	**X**	**X**		
Other Clinical Assessments								
12-lead ECG	**X**		**Day 1 of Cycles 4, 7, 10, 13, and as clinically indicated thereafter.**			**X**		Standard 12-lead ECG performed locally. Hypokalemia should be corrected (and normalization confirmed) prior to ECG collection. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Repeat if clinically indicated.
Cardiac ECHO or MUGA scan	**X**							Repeat if clinically indicated.
Adverse event assessment	Continuous from time of Informed Consent Form signature until 30 days after the last dose of study treatment.						**X**	- Grading via CTCAE version 5.0 (NCI 2017). - After V801, only SAEs that are related to study regimen or protocol procedure will be collected. - All drug- or procedure-related AEs and SAEs should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up. In LTFU, frequency of evaluation is left to the judgment of the investigator.

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		Every Cycle Day 1	Cycle 1 & Cycle 2 Day 15	Cycle 3 Day 15	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
Post-discontinuation anticancer therapies						X	X	Collect until death, withdrawal of consent, or study completion.
Survival assessment						X	X	Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures are required. This should be collected at minimum every 90 (±14) days if no other procedures are performed.
Tumor Assessment and Symptomatic Progression								
Brain MRI or CT	X		**Every 12 weeks for the first 24 weeks and every 16 weeks thereafter.** Scheduled based on C1D1, imaging should be performed according to			X	X	Screening brain MRI or CT is only required for participants with suspected CNS metastases or history of treated CNS metastases. Screening is not required for asymptomatic patients. - Only patients with a history of pretreated CNS metastases require subsequent on study brain imaging - Unscheduled and more frequent assessments if clinically indicated.

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		**Every Cycle** **Day 1**	**Cycle 1 & Cycle 2** **Day 15**	**Cycle 3** **Day 15**	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
CT or MRI of chest, abdomen, and pelvis **AND** Whole-body bone scan	**X**		calendar days, **independent of cycle delays** (that is, Week 13, Week 25, then Week 41, Week 57...) Imaging should be performed within 14 days of discontinuation from study intervention due to symptomatic progression if no radiographic progression (unless prior scans were performed ≤ 14 days)			**X**	**X**	- Perform within 7 days prior to the scheduled assessment (except in screening period). - Both CT/MRI AND bone scans are required at screening and all subsequent tumor assessments regardless of location of metastasis. - All CT/MRI and bone scans must be submitted to the sponsor-designated facility for BICR. Any pre-baseline scans documenting metastatic disease (including PSMA-PET/CT scans) will be collected and stored for central review. See Section 8.1 and refer to imaging manual for additional details. - CT/MRI and bone scans performed as part of routine care are acceptable as baseline assessments if done within 28 days prior to randomization and available for BICR as noted above. - Unscheduled assessments if signs and/or symptoms of disease progression are observed. - Participants discontinuing treatment prior to documented radiographic progression will continue to have scheduled disease assessments (that is, every 12 or 16 weeks) until documented radiographic progression.
Symptomatic progression			**X**			**X**	**X**	Assess: - Symptomatic Skeletal Event, defined as cancer-related symptomatic fracture, surgery or radiation to bone, or spinal cord compression. - Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anticancer therapy. - Development of clinically significant symptoms due to locoregional tumor progression requiring surgical intervention or radiation therapy. Note: Participants discontinuing treatment for reason other than symptomatic progression will continue to be followed for the development of symptomatic progression during Short-Term and Long-Term Follow-Up.
Exploratory Biomarker and Genetic Samples (blood and tumor tissue). See Section 1.3.1 for sampling schedule.								

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		**Every Cycle** **Day 1**	**Cycle 1 & Cycle 2** **Day 15**	**Cycle 3** **Day 15**	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
Pharmacokinetics. See Section 1.3.1 for PK sampling schedule and patient diary.								
Patient dosing diary			C1D1, C2D1, and C3D1					- Review diary C1D1 through C3D1. - After Cycle 3 Day 1, the diary is no longer required.
Patient-Reported Outcomes								
Worst Pain NRS			**Day 1 of every cycle through Cycle 13; then every 4 cycles thereafter** (C17D1, C21D1, C25D1, C29D1 etc.)			**X**		All PRO assessments will be self-reported by participant and should be completed before significant interaction with site personnel and administered in the following order: Worst Pain NRS, FACT-P, EQ-5D-5L, and PRO-CTCAE.
FACT-P						**X**		
EQ-5D-5L						**X**		
PRO-CTCAE						**X**		
Study Treatment								
Register visit with IWRS	**X**							Study patient number is assigned at registration.
Assign treatment via IWRS	**X**							Treatment assigned at randomization ≤ 7 days prior to Cycle 1 Day 1 after meeting eligibility.
Dispense abemaciclib/ placebo			See instructions					- Dispensed via IWRS. - Cycle 1 through Cycle 12: dispensed on Day 1 of every cycle. - Cycle 13 and beyond: dispensed on Day 1 every 2 cycles (C13D1, C15D1 etc.). - Participants will return used bottles on Day 1 of clinic visits for drug accountability. - See Section 6.2.1 for details.
Abemaciclib/ placebo			CCI [redacted] on Days 1 through 28 of a 28-day cycle.					
Abiraterone			Once daily on Days 1 through 28 of a 28-day cycle.					

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		**Every Cycle** **Day 1**	**Cycle 1 & Cycle 2** **Day 15**	**Cycle 3** **Day 15**	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
Prednisone			Once daily on Days 1 through 28 of a 28-day cycle.					Prednisolone may be used in lieu of prednisone per local abiraterone prescribing information or where prednisone is not commercially available.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BICR = blinded independent-central review; C1D1 = Cycle 1 Day 1; CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance score (Oken et al. 1982); EQ-5D-5L = European Quality of Life – 5 dimensions – 5 level; FACT-P = Functional Assessment of Cancer Therapy – Prostate Cancer; IWRS = interactive web-response system; LTFU = long-term follow-up; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition scan; NCI = National Cancer Institute; NRS = numeric rating scale; PET = positron emission tomography; PK = pharmacokinetics; PRO = patient-reported outcome; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; QD = once daily; SAE = serious adverse event.

a Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events at the participant's request or if deemed necessary by the investigator.

b Short-term follow-up begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (± 7 days), prior to start of a new anticancer therapy.

1.3.1. Sampling Schedule for Biomarkers, Genetics and Pharmacokinetics

Pharmacokinetics samples

Pharmacokinetic samples will be collected as specified in the table below. Samples will be analyzed for concentrations of abemaciclib and its active metabolites, M2 and M20.

The time and date of the PK sample draw should be recorded on the laboratory requisition form. Deviation from the specified sampling scheme is permitted when practical and logistical concerns arise.

During the PK sampling period (Cycle 1 Day 1 until Cycle 3 Day 1), participants will complete a Patient Dosing Diary to record the time and date of all blinded study drug doses. Dosing times should be entered into the eCRF for doses taken on

- the morning of the planned PK collection, and
- the morning and evening doses taken the **day before** the planned PK collection (Cycles 2 and 3).

Biomarkers and Genetics samples

Biomarkers and genetics samples will be collected as specified in the table below.

Biomarkers, Genetics and Pharmacokinetics Sampling Schedule

Sampling Day	Biomarkers and Genetics			Pharmacokinetics	
	Tumor Tissue	Plasma (Streck)	Whole Blood (Genetics)	Microsample PK	Plasma PK
Screening	X[a]				
Cycle 1 Day 1		X	X[b]	Post-dose: Anytime between 1 hour after the initial dose of blinded study drug and prior to the second dose of the day	Within ±10 minutes of microsample
Cycle 2 Day 1				Pre-dose[c] Post-dose: Anytime between 4 hours after the first daily dose of blinded study drug and prior to the second dose of the day[d]	
Cycle 3 Day 1				Pre-dose[c]	Within ±10 minutes of microsample
Cycle 4 Day 1		X			
Cycle 7 Day 1		X			
End of Treatment or Short-Term Follow-Up (V801) (prior to new anticancer therapy)	X[e]	X			

a Archival tumor sample will be collected, where available. The most recent sample is desired. Metastatic sample where available is preferred over primary tumor. Soft tissue as well as bony metastatic lesions are acceptable. The tumor samples will preferably be in the form of a formalin-fixed, paraffin embedded block. If this is not possible, approximately 20 slides of freshly prepared unstained 5-micron sections from the archival tumor block may be provided. Samples can be collected at any time during study if not collected at screening.
b Whole blood: collect once. Sample can be collected at a subsequent timepoint if not collected at Cycle 1 Day 1.
c Participants should refrain from taking blinded study drug until arrival at the clinic. Blinded study drug administration may resume following the PK sample draw.
d Sample may be collected by the participant or caregiver, as mutually agreed upon by the investigator and participant.
e Tumor tissue collection at the time of on-study radiographic progression is optional. A fresh metastatic biopsy (formalin-fixed and paraffin embedded) may be taken at the time of on-study radiographic progression, prior to start of new anticancer therapy if the investigator deems this to be appropriate and safe. Biopsy of a progressing metastatic lesion is preferred whenever possible. Soft tissue as well as bony metastatic lesions will be considered acceptable. If patient discontinues study for reasons other than radiographic progression, the biopsy should be considered only if the patient has completed at least 4 cycles of study treatment.

1.3.2. Continued Access SoA

Continued-Access Schedule of Activities

Visit	Continued Access Treatment[a] 501-5XX	Follow-Up[b] 901	
Procedure[c]			**Instructions**
Adverse events collection	X	X	Grading via CTCAE, Version 5.0. Frequency of evaluation, including efficacy assessments, is left to the judgment of the investigator based on standard of care.
Administer abemaciclib	X		Take prescribed dose CCI on Days 1 through 28 of a 28-day cycle. Abemaciclib can be administered every 28 ± 3, 56 ± 3, or 84 ± 3 days at investigator discretion. Up to 3 cycles of abemaciclib dosage may be dispensed at a time.
Administer abiraterone	X		Take prescribed dose QD on Days 1 through 28 of a 28-day cycle. Abiraterone supplied by sponsor can be administered every 28 ± 3, 56 ± 3, or 84 ± 3 days at investigator discretion. In cases of site sourced abiraterone, frequency of dispensing is left to the judgment of the investigator based on standard of care.
Administer prednisone[d]	X		Take prescribed dose QD on Days 1 through 28 of a 28-day cycle. Prednisone supplied by sponsor can be administered every 28 ± 3, 56 ± 3, or 84 ± 3 days at investigator discretion. In cases of site sourced prednisone, frequency of dispensing is left to the judgment of the investigator based on standard of care.

Abbreviations: CCI [redacted] CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; QD = once daily.

a IP will be dispensed at a maximum of every 3 cycles (84 ± 3 days). Additional visits may be performed as clinically indicated.

b Continued-access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

c Efficacy assessments will be done at the investigator's discretion based on the standard of care.

d In this protocol prednisone implies prednisone or prednisolone.

2. Introduction

2.1. Study Rationale

Abemaciclib is an oral selective inhibitor of CDK4 & 6 that is administered on a continuous schedule. Abemaciclib is approved globally for the treatment of HR+, HER2-, advanced or metastatic breast cancer based on improvements in PFS when added to endocrine therapy (Sledge et al. 2017; Johnston et al. 2019). Abemaciclib is also approved in selected geographies including the US as single-agent therapy for the treatment of HR+, HER2- metastatic breast cancer (Dickler et al. 2017). OS benefit has been confirmed for abemaciclib in combination with fulvestrant (Sledge et al. 2020) in endocrine-resistant metastatic breast cancer. Recently, the addition of abemaciclib to adjuvant endocrine therapy in patients with high-risk node positive HR+, HER2- early-stage breast cancer demonstrated significant reduction in the risk of recurrence, including robust improvements in IDFS and DRFS (Johnston et al. 2020; Harbeck et al. 2021). These data are the basis for several regulatory approvals, including in the US.

The activity of abemaciclib in prostate cancer is currently being investigated in several clinical studies including:

- I3Y-MC-JPCM (CYCLONE 2), a Phase 2/3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone with or without abemaciclib in patients with metastatic castration-resistant prostate cancer [NCT03706365].
- I3Y-MC-JPCY (CYCLONE 1), A Phase 2 study of abemaciclib in metastatic castration-resistant prostate cancer patients previously treated with a novel hormonal agent and taxane-based chemotherapy [NCT04408924].

The treatment landscape of mHSPC has evolved in recent years. The addition of docetaxel chemotherapy, abiraterone, enzalutamide, or apalutamide to ADT significantly improves outcomes of patients with mHSPC (Sweeney et al. 2015; James et al. 2016; Fizazi et al. 2017; James et al. 2017; Armstrong et al. 2019; Chi et al. 2019; Davis et al. 2019). However, despite significant advances in therapy, patients with high-risk/high-volume disease have a poorer prognosis with shorter time to progression and survival (Kyriakopoulos et al. 2018; Clarke et al. 2019; Fizazi et al. 2019; Hoyle et al. 2019; Chowdhury et al. 2021). Thus, there is a pressing

medical need for novel treatment approaches in this subgroup of patients who may benefit from early treatment intensification with new combination therapy.

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CYCLONE 3 is a, multicenter, multinational, randomized, double-blind, placebo-controlled Phase 3 study to assess the safety and efficacy of adding abemaciclib to abiraterone plus prednisone in men with high-risk mHSPC. High-risk is defined as the presence of ≥4 bone metastases and/or ≥1 visceral metastases.

2.2. Background

2.2.1. Metastatic Hormone-Sensitive Prostate Cancer

Prostate cancer is a leading cause of mortality and morbidity globally and represents a substantial public health burden. With nearly 1.4 million new cases and 375,000 deaths worldwide, prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men in 2020 (Sung et al. 2021). The incidence and stage at diagnosis vary substantially across the world and is strongly correlated to local PSA screening programs.

Metastatic hormone-sensitive prostate cancer is incurable and describes the clinical situation, whereby, a patient with metastatic prostate cancer has either never received treatment with ADT or exhibits ongoing sensitivity to ADT. Men with mHSPC have either primary progressive metastatic disease or present with metastases at diagnosis (de novo mHSPC). Approximately 30% of men diagnosed with localized prostate cancer will develop metastases (Hahn et al. 2017). De novo metastatic disease accounts for 7% of diagnosed cases in the US, ~20% in France and UK and up to 60% in Asia (SEER Cancer Stat Facts: prostate [WWW]; INCa prostate cancer page [WWW]; Chen et al. 2014; NICE 2020).

While ADT alone has been the standard of care for mHSPC for decades, the treatment landscape has rapidly evolved in recent years. Several treatments, including docetaxel, abiraterone, enzalutamide, and apalutamide, have each demonstrated survival benefit when used upfront with ADT.

Docetaxel

The benefit of adding docetaxel to ADT for mHSPC was established by the CHAARTED and STAMPEDE (Arm C) trials (Sweeney et al. 2015; James et al. 2016).

The CHAARTED study was the first study to demonstrate that adding docetaxel to ADT in men initiating treatment for mHSPC prolongs survival (Sweeney et al. 2015). The median OS was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 months vs. 44.0 months; HR: 0.61). This survival benefit only reached significance in patients with high-volume defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis (HR: 0.60; CI: 0.45–0.81; $p < 0.001$), but not in low-volume disease (HR: 0.60; CI: 0.32–1.13). The addition of docetaxel also led to significant improvements in secondary endpoints, such as the time to development of castration-resistant prostate cancer and time to clinical progression, with the benefit more pronounced in all cases among patients with

high- rather than low-volume disease (Sweeney et al. 2015). In a long-term survival analysis of the CHAARTED study, after a median follow-up of 53.7 months, the median OS was 57.6 months for ADT plus docetaxel vs. 47.2 months for ADT alone (HR: 0.72) (Kyriakopoulos et al. 2018). The survival benefit was confirmed for high-volume disease (51.2 vs. 34.4 months, HR: 0.63) but there was still no evidence of an OS benefit in low-volume disease (63.5 months vs. NR, HR: 1.04).

The multi-arm STAMPEDE trial also showed a survival benefit in the M1 subgroup (Arm C), with the addition of docetaxel to standard of care (HR: 0.76) (James et al. 2016). A retrospective analysis according to disease volume based on the CHAARTED definition confirmed the benefit in survival for upfront docetaxel at longer follow-up, however, there was no evidence of heterogeneity of treatment effect on survival over metastatic burden sub-groups (high volume: HR: 0.81, p=0.064; low volume: HR: 0.76, p=0.107; interaction p= 0.827) (Clarke et al. 2019). STAMPEDE also recruited more patients with de novo metastatic disease (~95% vs. 73%), representing a different natural history of the disease and thereby, possibly explaining the differential response to therapy.

Abiraterone

Two separate trials (LATITUDE and STAMPEDE Arm G) demonstrated the addition of abiraterone acetate to ADT significantly improved OS in the mHSPC setting.

LATITUDE enrolled all newly diagnosed patients with at least 2 of 3 risk factors: a Gleason score of ≥8, ≥3 bone metastases, or the presence of measurable visceral metastasis. The median rPFS was 33.0 months in the abiraterone group and 14.8 months in the placebo group (HR: 0.47) (Fizazi et al. 2017). After a median follow-up of 51.8 months, the median OS was significantly longer in the abiraterone group than in the placebo group (53.3 vs. 36.5 months; HR: 0.66) (Fizazi et al. 2019). In a post hoc analysis patients were stratified based on disease volume, defined using the CHAARTED criteria. In patients with high-volume disease, abiraterone improved rPFS by 19 months (33.1 vs. 14.7 months; HR: 0.46) and OS by 16 months (49.7 vs. 33.3 months; HR: 0.62). In the low-volume subgroup, abiraterone improved rPFS (49.8 vs. 22.4 months; HR: 0.59) but not OS (not reached in either arm; HR: 0.72, p=0.1242) (Fizazi et al. 2019). However, the proportion of low-volume disease patients was relatively small (~20%, 243 of 1199 patients) and, importantly, the study was not powered for this subgroup analysis.

Data from STAMPEDE (Arm G) confirms the survival advantage of adding abiraterone to standard ADT (HR: 0.61) (James et al. 2017). Notably, this benefit was also observed when stratified by LATITUDE low- or high-risk criteria (HR: 0.66 and HR: 0.54; p-interaction = 0.39), or CHAARTED low- or high-volume disease (HR: 0.64 and HR: 0.60; p-interaction = 0.77) (Hoyle et al. 2019).

More recently, PEACE 1, a Phase 3 randomized study with a 2x2 factorial design, evaluated the addition of abiraterone plus prednisone and/or local RT to standard therapy with ADT ± docetaxel in men with de novo mHSPC. In the overall population, rPFS and OS were significantly improved with abiraterone (rPFS: 4.5 vs. 2.2 years, HR: 0.54 and OS: 5.7 vs. 4.7 years, HR: 0.82) (Fizazi et al. 2021a, 2021b). Similarly, in the subgroup of patients who received docetaxel (60%, n=710, among whom 64% had high disease volume), Fizazi et al reported the addition of abiraterone improved both rPFS and OS rPFS: 4.5 vs. 2.0 years, HR: 0.50 and OS:

NE vs. 4.4 years, HR: 0.75). Survival benefits were consistent across subgroups analyzed, including the high-volume group (rPFS: 4.1 vs. 1.6 years, HR: 0.47 and OS: 5.1 vs. 3.5 years, HR: 0.72). The rPFS in low-volume was improved rPFS: NE vs. 2.7 years, HR: 0.58), however, survival data are currently immature for this group.

Enzalutamide and apalutamide

Three randomized Phase 3 trials, ENZAMET, ARCHES, and TITAN demonstrated that early treatment intensification with the addition of novel androgen receptor antagonists, enzalutamide or apalutamide, to ADT delayed time to progression and improved OS in mHSPC patients with relapsed or de novo disease (Armstrong et al. 2019; Chi et al. 2019; Davis et al. 2019).

However, it is unclear if the observed OS benefit is maintained irrespective of disease volume or risk, and none of these studies was powered for detecting a heterogeneity of effect. The ENZAMET analysis favored a survival benefit of enzalutamide in low-volume disease group while ARCHES favored the high-volume (Davis et al. 2019; Armstrong et al. 2021). In TITAN, subgroup analyses favored a survival benefit of apalutamide in the high-volume and high-risk groups (Chi et al. 2019; Ozguroglu et al. 2020).

ENZAMET allowed the use of concurrent docetaxel, while ARCHES and TITAN permitted prior treatment with up to 6 cycles of docetaxel, representing 45%, 18%, and 11% of the respective trial populations. Data from subgroup analyses are yet unclear on the benefit of adding docetaxel to enzalutamide or apalutamide, warranting further follow-up. More mature data from the ENZAMET study and initial data from the ARASENS study (darolutamide with docetaxel; NCT02799602) are awaited to help clarify the role of androgen receptor inhibitors when combined with docetaxel.

Medical need

High disease burden is considered an independent prognostic factor for mHSPC (Francini et al. 2018) and plays an important role when selecting appropriate treatments. Based on most current guidelines, ADT with abiraterone, apalutamide, enzalutamide or docetaxel are acceptable treatment options for the intended study population. While outcomes of patients presenting with de novo or recurrent high-risk/volume mHSPC were improved with combination therapy, this group of patients still experiences shorter time to progression to castration-resistant disease and dismal survival compared to the low-risk/volume group. Thus, there is a pressing unmet need for novel treatment approaches, particularly in this poor prognosis group of patients for whom early treatment intensification has the potential to demonstrate clinically meaningful improvements.

This Phase 3, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of adding abemaciclib to abiraterone plus prednisone in patients with high-risk mHSPC.

2.2.2. Abemaciclib

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (Sherr 1996; Ortega et al. 2002). The CDKs 4 and 6 participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point by phosphorylating and inactivating the Rb tumor-suppressor protein.

Alterations in this pathway occur frequently in human cancers and involve (1) loss of CDK inhibitors by mutation or epigenetic silencing, (2) mutation/overexpression of either CDK4 and

CDK6 or cyclin D, or (3) inactivation of Rb. These alterations render cells less dependent on mitogenic signaling for proliferation. Apart from those tumors with complete inactivation of Rb, which functions downstream of the CDK4 and CDK6–cyclin D complex, all of these cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small-molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of CDK4 & 6 that is administered on a continuous dosing schedule. The clinical activity of abemaciclib has been extensively studied in HR+, HER2- advanced and MBC, and most recently as adjuvant therapy in high-risk node positive HR+ HER2- early-stage breast cancer.

Abemaciclib monotherapy demonstrated meaningful antitumor activity in heavily pretreated hormone refractory HR+, HER2- metastatic breast cancer with response rates of 19.7% and 28.6% observed in the Phase 2 single-arm study MONARCH 1 (NCT02102490) and in the Phase 2 randomized study nextMONARCH (NCT02747004), respectively (Dickler et al. 2017; Hamilton et al. 2019).

In MONARCH 2, a Phase 3 randomized, placebo-controlled study (NCT02107703), the addition of abemaciclib to fulvestrant significantly improved PFS compared to fulvestrant alone (16.4 months vs. 9.3 months, HR: 0.553; 95% CI: 0.449, 0.681). In patients with measurable disease, abemaciclib plus fulvestrant achieved an ORR of 48.1% (95% CI, 42.6% to 53.6%) compared with 21.3% (95% CI, 15.1% to 27.6%) in the control arm (Sledge et al. 2017). Importantly, OS was significantly improved in the abemaciclib arm compared to the control arm (46.7 months vs. 37.3 months, HR: 0.76; 95% CI, 0.61-0.95), and this survival benefit was consistent across subgroups, including patients with visceral metastases (Sledge et al. 2020).

In the Phase 3 randomized, placebo-controlled MONARCH 3 study (NCT02246621), the addition of abemaciclib to a nonsteroidal AI as initial treatment of HR+, HER2− advanced breast cancer provided a significant improvement in PFS (28.2 months vs. 14.8 months; HR: 0.54; 95% CI: 0.42 to 0.70) and ORR (measurable disease: 61.0% vs. 45.5%) compared to placebo plus AI (Johnston et al. 2019). The OS data from this study continue to mature.

In monarchE, a Phase 3 randomized, open-label study (NCT03155997), abemaciclib was studied in combination with adjuvant endocrine therapy in patients with high-risk, node positive HR+ HER2- early-stage breast cancer. At the time of primary analysis (Johnston et al. 2020), after a median follow up of 19 months, patients treated with abemaciclib plus adjuvant endocrine therapy demonstrated a 29% reduction in the risk of recurrence (HR: 0.71, 95% CI: 0.58 to 0.87; p=.0009) Likewise, after 27 months of follow-up, improved rates of IDFS and DRFS were maintained (Harbeck et al. 2021).

The most common adverse reactions for abemaciclib (incidence ≥20%) are diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia (Verzenio package insert, 2021).

Abemaciclib (VERZENIO[S]) is currently approved for the treatment of HR+ HER2− breast cancer. For details see local prescribing information.

Details on the safety profile of monotherapy abemaciclib as well in combination with other agents are available in the IB.

2.2.3. Abiraterone

Abiraterone, the active metabolite of abiraterone acetate, irreversibly inhibits cytochrome P450 (CYP)17 (17α-hydroxylase/C17, 20-lyase), an essential enzyme in androgen biosynthesis that is expressed in testicular, adrenal and prostatic tumor tissues. Abiraterone acetate is approved in combination with prednisone for the treatment of patients with high-risk mHSPC and mCRPC (abiraterone acetate package insert, 2020).

For more information, refer to the abiraterone prescribing information.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of abemaciclib can be found in the IB. Information on AEs expected to be related to abemaciclib can be found in IB. Information on SAEs expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate periodically during the course of the study and may be found in the IB.

More detailed information about the known and expected benefits and risks of abiraterone, prednisone (or prednisolone), and background therapy with LHRH agonists/antagonists may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

2.3.1. Risk Assessment

Study Intervention

This study aims to compare the efficacy and safety of abemaciclib and abiraterone plus prednisone (experimental arm) versus placebo and abiraterone plus prednisone (control arm) in participants with high-risk mHSPC. All participants will receive an established active treatment with abiraterone plus prednisone and will continue ADT throughout the study. Abiraterone plus prednisone as the control arm reflects an acceptable treatment option for high-risk mHSPC per ESMO and NCCN guidelines (Parker et al. 2020; NCCN 2022).

Hematology, hepatic, and renal function tests will be regularly monitored throughout the study in accordance with abemaciclib and abiraterone prescribing information. Increased susceptibility to infection will be monitored with regular hematology monitoring. These activities enable appropriate investigator oversight for identification and management of AEs.

Appropriate safety assessments, on-study monitoring, and AE management are detailed in Section 8.3 and in the SoA in Section 1.3.

Study Procedures

Detailed schedule of study procedures is in Section 1.3.

Participants will undergo regularly scheduled blood draws by venipuncture, which is common in clinical practice with low risks of complications.

To ensure optimal management of AEs and maximize supportive care, dose adjustment for AEs of abemaciclib/placebo and abiraterone, along with specific guidelines on management for ADRs (hematologic toxicities, diarrhea, ALT/AST increased, ILD/pneumonitis, VTE, hypertension, adrenal insufficiency, and hypoglycemia) are provided in the protocol.

Participants will undergo regular radiological imaging to assess for clinical benefit as per international guidelines (Mottet et al. 2021; NCCN 2022). The 12- and 16-weeks imaging intervals used in this study appear reasonable and are consistent with PCWG3 recommendations in metastatic prostate cancer clinical trials. The investigator in conjunction with guidance provided in Section 1.3 and Section 10.9, Appendix 9 will select appropriate imaging study.

An independent DMC will be commissioned to review the safety and efficacy of the treatment combination and make recommendations as to the future conduct of the study. The sponsor will monitor blinded data on an ongoing basis with the intent of early safety signal identification and risk minimization.

2.3.2. Benefit Assessment

Despite therapeutic advances in mHSPC, there is still a pressing unmet medical need for tailored treatment approaches, particularly for patients with high-risk disease who experience shorter survival outcomes with current approved treatments. For these high-risk patients, early treatment intensification with novel combination therapy has the potential to meaningfully improve clinical outcomes.

Abemaciclib is a potent and selective oral inhibitor that has demonstrated significant clinical benefit and improved overall survival in HR+, HER2- metastatic breast cancer, including subgroups with adverse prognostic factors. CCI [redacted]

All participants will receive active background therapy with abiraterone plus prednisone and will continue ADT throughout the study. CCI [redacted]

2.3.3. Overall Benefit Risk Conclusion

The potential risks of abemaciclib in combination with abiraterone plus prednisone are justified in consideration of the measures to minimize these risks and the anticipated benefit of improved disease control, as measured by improved rPFS in participants with high-risk mHSPC, an incurable disease with a poor prognosis. For these high-risk patients, early intensification with this novel combination therapy has the potential to meaningfully improve clinical outcomes.

Taking into account the above measures, it is determined that the potential risks to the participants are reasonable in relation to the anticipated benefits for participating in the study.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To determine whether adding abemaciclib to abiraterone plus prednisone[a] improves radiographic progression-free survival (rPFS).	• rPFS assessed by the investigator.
Secondary	
• To evaluate improvements in other clinically relevant efficacy endpoints with the addition of abemaciclib to abiraterone plus prednisone.	• rPFS by blinded, independent, central review (BICR) • Clinical PFS (cPFS) • Castration-resistant prostate cancer (CRPC)-free survival • Time to symptomatic progression • Time to PSA progression • Time to initiation of new anticancer therapy • Overall survival (OS).
• To characterize the safety of adding abemaciclib to abiraterone plus prednisone.	• The safety endpoints evaluated will include, but are not limited to, the following: AEs, TEAEs, SAEs, clinical laboratory tests, ECGs, vital signs, and physical examinations.
• To characterize the PK of abemaciclib when administered in combination with abiraterone.	• Concentrations of abemaciclib.
• To assess patient-reported pain and HRQoL.	• Time to pain progression • Time to deterioration in HRQoL measured by the FACT-P (Physical Well-Being and PCS scores) and EQ-5D-5L.
Exploratory	
CCI	

Abbreviations: AE = adverse event; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life – 5 dimensions – 5 level; HRQoL = Health-related quality of life; FACT-P = Functional Assessment of Cancer Therapy-Prostate; PK = pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Prednisone implies prednisone or prednisolone.

Primary estimand

The primary research question is: What is the difference in rPFS when adding abemaciclib or placebo to abiraterone plus prednisone in patients with high-risk mHSPC?

The estimand for the primary objective is described by the following attributes:

- Population: adult men with high-risk mHSPC randomized to study arms (primary analysis population). Further details can be found in Section 5.
- Endpoint: investigator-assessed rPFS in the primary analysis population, which is defined as the time from randomization until
  - first occurrence of documented radiographic disease progression, or
  - death from any cause.
- Treatment condition: Abemaciclib CCI and abiraterone CCI plus prednisone CCI will be compared to placebo CCI and abiraterone 1CCI plus prednisone CCI. Study intervention will be administered until radiographic progression, unacceptable toxicity, or until other discontinuation criteria are met (see Section 7.1). Further details on study intervention, concomitant therapy, and dose modification, can be found in Section 6.
- Intercurrent-event strategies (IES):
  - Study intervention discontinuation prior to radiographic progression or death without prior progression is handled with CCI
  - The initiation of new anticancer therapy prior to documented disease progression or death without prior progression is handled with CCI
  - Extended time without adequate assessment prior to documented disease progression or death without prior progression is handled with CCI
- Population-level summary measure: Hazard ratio of rPFS in the experimental arm versus the control arm estimated using a stratified Cox regression model (Cox 1972).

- Rationale for IES: The interest lies in the treatment effect regardless of study intervention discontinuation and without the confounding effect of the start of a new anticancer therapy or extended time without adequate assessment.
    - Study intervention discontinuation due to reasons other than documented radiographic disease progression or death without prior progression is handled with CCI Time from randomization until documented disease progression or death without prior progression regardless of study intervention discontinuation will be considered in the analysis.
    - The initiation of new anticancer therapy could happen prior to observing an rPFS event and potentially confound the assessment of the primary endpoint. CCI
    - Disease progression observed after an extended time without adequate tumor assessment may have occurred much earlier but is not reported because the scheduled assessment was not done. This inadequate observation may introduce bias to rPFS estimates. If extended time without adequate assessment occurs, CCI

4. Study Design

4.1. Overall Design

CYCLONE 3 is a multicenter, multinational, randomized, double-blind, placebo-controlled, Phase 3 study to assess the safety and efficacy of adding abemaciclib to abiraterone plus prednisone in patients with high-risk mHSPC. High-risk is defined as the presence of ≥4 bone metastases and/or ≥1 visceral metastases.

Approximately 900 participants (see Section 5 for study population) will be randomized in a 1:1 ratio.

Treatment Arms:

Abiraterone and prednisone (or prednisolone):

All participants will receive therapy with abiraterone [redacted] plus prednisone [redacted]
Prednisolone may be used in lieu of prednisone per local abiraterone prescribing information or where prednisone is not commercially available.

Blinded study drug:

- Experimental arm: Abemaciclib [redacted] orally [redacted] The dose has been determined in the Phase 2/3 Study CYCLONE 2 (see Section 4.3).
- Control arm: Placebo [redacted] orally [redacted]

Abiraterone, prednisone, and abemaciclib/placebo, will be initiated ≤7 days following randomization and administered on Days 1 through 28 of a 28-day cycle until disease progression, unacceptable toxicity, or other discontinuation criteria are met (see Section 7.1). Details on treatment administration are described in Section 6.1.

Note: Participants who have not undergone bilateral orchiectomy are required to continue background ADT with an LHRH agonist/antagonist throughout the study.

Stratification:

Randomization will be stratified according to the following factors:

- de novo metastatic prostate cancer (metastatic disease at initial diagnosis) (Yes vs. No).
- visceral metastases (Yes vs. No).

These stratification criteria were selected because they represent important prognostic factors and/or an imbalance that may bias study results.

Primary endpoint:

The primary endpoint of the study is investigator-assessed rPFS or death from any cause, whichever occurs first. Other study endpoints are listed in Section 3.

Planned analyses with detailed descriptions are listed in Sections 9.4.2 and 9.4.3.

Participants will be monitored throughout the study for safety and have procedures performed as outlined in the SoA (see Section 1.3).

All participants discontinuing study treatment will enter the short- and long-term follow-up periods and have procedures performed as shown in the SoA (Section 1.3), except those lost to follow-up, the participant withdrew consent or died.

In addition, participants discontinuing treatment prior to documented radiographic progression will continue to have scheduled disease assessments until documented radiographic progression and will be followed for the development of symptomatic progression.

Participants discontinuing treatment due to documented radiographic progression will be followed for the development of symptomatic progression.

All patients will be followed for survival.

Illustration of the study design is in Section 1.2.

4.2. Scientific Rationale for Study Design

The overall rationale for the study is described in Section 2.1. Specific design aspects are discussed below:

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. The eligibility criteria were carefully considered to ensure the enrolled participants are representative of patients with high-risk mHSPC, minimizing heterogeneity while maintaining clinical relevance and alignment with current treatment guidelines. Therefore, patients will be stratified for key factors associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses.

Investigational drug administration in this study is double-blind and is placebo controlled. This implies that patients are blinded to their treatment assignment and that investigational sites and the sponsor study team do not have immediate access to treatment assignments for any patients. These design features further minimize potential bias due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients.

Delaying the emergence or the progression of radiographically detectable distant metastases is a clinically relevant endpoint for the determination of the benefit of the study treatment that is not impacted by post-treatment anticancer therapies. Therefore, the selected primary endpoint of the study is investigator-assessed rPFS, which takes into account specificities of metastatic prostate cancer which is a heterogeneous disease that progresses through multiple clinical steps with a high prevalence of bone metastases. Progression of metastatic bone disease is of paramount clinical importance since it is responsible for the severe morbidity of skeletal-related events such as symptomatic fractures, pain, surgery or palliative radiation to bone, and spinal cord compression.

Response Evaluation Criteria in Solid Tumors, Version 1.1 designates numerous lesions as nonmeasurable. These include bone metastases without a soft tissue component measuring ≥10 mm (the large majority of bone metastases). Conventional RECIST also lacks provisions to

differentiate true progression of bone metastasis from the flare, a paradoxical worsening of the bone scan attributed to bone healing as a result of a favorable antitumor effect.

To ensure consistent and reproducible assessment of rPFS and control for tumor flare, criteria for defining progression of disease by bone scans have been developed by the Prostate Cancer Clinical Trials Working Group (PCWG) and used widely in metastatic prostate cancer randomized trials.

In this study, the consensus guidelines of the RECIST 1.1 for soft tissue and the PCWG for bone are taken into consideration and adapted for this high-risk mHSPC patient population for the determination of rPFS. The rPFS (which also includes death from any cause) will be assessed by the investigator/local radiologist for the primary endpoint, and rPFS by BICR will be evaluated as a secondary endpoint.

To complement the primary endpoint of rPFS, other clinically relevant aspects of disease progression such as symptomatic progression, PSA progression, and the initiation of new anticancer therapy are assessed in secondary endpoints. Importantly, OS will also be assessed as a secondary endpoint. At the time of the rPFS primary outcome, it is likely that OS will be immature. However, given the positive correlation between disease progression and OS for patients with metastatic prostate cancer (Rathkopf et al. 2018; Maeda et al. 2021, Woo et al. 2021), it is anticipated that a clinically relevant benefit in rPFS is expected to translate into a survival benefit with longer follow-up.

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race and/or ethnicity.

4.3. Justification for Dose

In CYCLONE 3, abemaciclib (or matched placebo) will be at administered at a dose of CCI in combination with abiraterone CCI plus prednisone CCI on a 28-day continuous dosing schedule.

Abemaciclib

The approved starting dose of abemaciclib in breast cancer is:

- 150 mg BID in combination with endocrine therapy, and
- 200 mg BID when given as a monotherapy.

However, data from previous clinical studies conducted in men and women suggested that men tolerate a higher dose of abemaciclib than women. In the Phase 1 monotherapy dose escalation Study I3Y-MC-JPBA, men reported lower GI toxicity rates than women: diarrhea (56.0% vs. 71.0%), nausea (41.3% vs. 51.1%), vomiting (22.7% vs. 35.9%), and abdominal pain (12.0% vs. 19.1%). Similarly, lower rates of GI toxicities in men versus women were also observed in a Phase 3 Study I3Y-MC-JPBK in patients with Stage IV non-small cell lung cancer. As a result, CYCLONE 2, a Phase 2/3 study evaluating abemaciclib/placebo in combination with abiraterone CCI plus prednisone/prednisolone CCI in patients with mCRPC (NCT03706365) included an initial safety lead in period where patients were randomized to abemaciclib/placebo CCI or CCI to determine the RP2D of abemaciclib for this study drug combination in prostate cancer patients. CCI

CCI

In a planned safety analysis of CCI

In patients with MBC, including those in MONARCH 2, a positive exposure-efficacy relationship was previously observed (Turner et al. 2018), which indicates patients with higher PK exposures are more likely to experience greater treatment benefit than those with lower exposures. CCI

Therefore, in CYCLONE 3, CCI was selected as the starting dose for abemaciclib/placebo in combination with abiraterone plus prednisone in high-risk mHSPC.

Abiraterone/Prednisone

The doses of abirateroneCCI and prednisone CCI were selected based on prescribing information for mHSPC.

4.4. End of Study Definition

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the evaluation of final OS data as determined by the sponsor. Investigators will continue to follow the study schedule for all participants until notified by the sponsor that study completion has occurred.

"End of study" refers to the date of the last visit or last scheduled procedure for the last participant. The end of trial occurs after study completion and after the last participant has discontinued study treatment and completed continued-access period follow-up (see Section 6.6).

5. Study Population

Participants must meet all inclusion criteria and none of the exclusion criteria. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

1. Adult men (≥18 years or age of majority per local regulation) willing and able to provide written informed consent and comply with study procedures (see in Section 10.1.3, Appendix 1).
2. Histologically confirmed predominant adenocarcinoma of the prostate. Well-differentiated neuroendocrine carcinoma, small cell or large cell neuroendocrine carcinoma, sarcomatoid, and carcinoid tumors are excluded.
3. High-risk metastatic hormone-sensitive prostate cancer documented on conventional imaging. High-risk is defined as:
    - ≥4 bone metastases by bone scan

      and/or
    - ≥1 visceral metastases (for example, liver, lung, and adrenal) by CT or MRI.

      - Local invasion (for example, bladder) or lymph node involvement does not qualify as visceral metastases. A previously irradiated visceral lesion as the sole site of disease can meet high-risk metastatic disease criteria provided there has been subsequent radiographic progression at that site.
4. Participants must have initiated ADT with LHRH agonist/antagonist or bilateral orchiectomy prior to randomization.
    - Up to 3 months of ADT prior to randomization is permitted with or without first-generation anti-androgen (for example, bicalutamide). The start of ADT is the earliest date an LHRH agonist/antagonist was administered, or date of surgical castration.
    - For participants receiving an LHRH agonist, first generation anti-androgens are allowed to continue for up to 2 weeks after Cycle 1 Day 1, all other use subsequent to Cycle 1 Day 1 is prohibited.
    - Participants who have not undergone a bilateral orchiectomy must continue the LHRH agonist/antagonist throughout the study.
5. For patients receiving bone-modifying agents (for example, bisphosphonates or denosumab) for the management of bone metastasis, dose must be stable for at least 4 weeks prior to randomization. This does not apply to patients on osteoporosis dosing.

6. Have adequate organ function, as defined below:

System	Laboratory Value
Cardiac	
LVEF	≥50%
Clinical Chemistry	
Serum albumin	≥3 g/dL
Serum potassium	≥3.5 mmol/L
Hematologic	
Absolute neutrophil count (ANC)	$\geq 1.5\times10^9$/L G-CSF should not be administered to meet criteria.
Platelets	$\geq 100\times10^9$/L Transfusion should not be administered to meet criteria.
Hemoglobin	≥9 g/dL (≥90 g/L) Transfusion should not be administered to meet criteria.
Hepatic	
Total bilirubin	≤1.5×ULN
ALT and AST	≤2.5×ULN
Renal	
eGFR (calculated per local clinical practice guidelines)	≥30 mL/min

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; G-CSF = granulocyte colony-stimulating factor; LVEF = left ventricular ejection fraction; ULN = upper limit of normal.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.
8. Participants with female partners of childbearing potential must agree to use a condom along with another effective contraception method during the study and for at least 3 weeks following the last dose of study treatment.

5.2. Exclusion Criteria

Participants are excluded from the study if ANY of the following criteria apply:

9. Known or suspected contraindications or hypersensitivity to abiraterone, prednisone/prednisolone, or abemaciclib or to any of the excipients; inability to swallow oral medications or gastrointestinal disorder affecting absorption.
10. Prior treatment with abemaciclib or any other CDK4 & 6 inhibitor.
11. Development of metastatic prostate cancer in the context of castrate levels of testosterone.
12. Received any prior systemic therapy for metastatic prostate cancer (including investigational agents), except for ADT and first-generation anti-androgen (see inclusion criterion [4]).

13. Radiation therapy to treat the primary prostate tumor in the context of metastatic disease and/or radiation or surgery to all metastatic lesions. One course of palliative radiation or surgical therapy is permitted if it was administered at least 2 weeks prior to randomization.
14. Untreated spinal cord compression, spinal metastases with emergent risk of spinal cord compression, or structurally unstable bone lesions at high-risk for impending fracture.
15. Known untreated CNS metastases or any history of leptomeningeal disease. Screening of asymptomatic patients for CNS metastases is not required. Note: Patients with a history of treated brain metastases by either surgery or radiation therapy are eligible provided that disease is stable following treatment for at least 8 weeks prior to randomization and with no requirement for corticosteroids for at least 2 weeks prior to randomization.
16. Serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).
17. Clinically significant cardiovascular disease as evidenced by myocardial infarction, arterial thrombotic events, or severe/unstable angina in the past 6 months, or New York Heart Association Class II to IV heart failure.
18. History of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Chronic and hemodynamically stable atrial arrhythmia well-controlled on medical therapy is permitted.
19. Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥95 mmHg). Patients with a history of hypertension are allowed provided BP is controlled by anti-hypertensive treatment.
20. Clinically active or chronic liver disease, moderate/severe hepatic impairment (Child-Pugh Class B and C), ascites, or bleeding disorders secondary to hepatic dysfunction.
21. History of adrenal dysfunction.
22. Had a major surgery within 2 weeks prior to randomization. All incisions must be healed or healing, aseptic and without signs or symptoms of infection.
23. Prior or active concurrent malignancy (with the exception of non-melanomatous skin cancer). Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and/or whose likelihood of recurrence is very low per investigator's judgment are eligible for this study. The Lilly CRP/CRS will approve enrollment of patients with prior malignancies in remission before these patients are enrolled.

24. Active systemic infections (for example, bacterial infection requiring intravenous [IV] antibiotics at time of initiating study treatment, fungal infection, or detectable viral infection requiring systemic therapy) or viral load (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]). Screening is not required for enrollment.
25. Have received live vaccination ≤ 4 weeks prior to randomization. Inactivated vaccines are permitted.
26. Current enrollment in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study. Have participated in any clinical trial for which treatment assignment is still blinded. If patient has participated in a clinical study involving an investigational product, 3 months or 5 half-lives (whichever is shorter) should have passed prior to randomization. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and the Lilly CRP/CRS is required to establish eligibility.

5.3. Lifestyle Considerations

The following lifestyle restrictions are applicable to all randomized patients:

- While on study, patients should refrain from consuming grapefruit and pomegranate fruits and/or juice, saw palmetto and other herbal/non-herbal products known to be strong inhibitors of CYP3A, have prostate cancer activity, or affect PSA levels.
- Participants with female partners of childbearing potential must agree to use a condom along with another effective contraception method during the study and for at least 3 weeks following the last dose of study treatment (see Section 10.4, Appendix 4).
- Participants should not donate blood or sperm during the study and for 3 months after the last dose of study treatment.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

The following participants may be eligible for rescreening:

- Participants who become eligible to enroll in the study because of a protocol amendment.
- Participants whose status has changed such that the eligibility criterion that caused the participant to screen fail would no longer cause the participant to fail screening again (for example, unexpected surgery during the screening period that is no longer relevant following recovery from surgery).

- A patient who completes screening and meets all inclusion and exclusion requirements but is unable to be enrolled due to extenuating circumstances (such as severe weather, death in family, child illness).

The interval between rescreening should be ≥2 weeks. Individuals may be rescreened a maximum of 2 times. Rescreened participants must sign a new ICF and will be assigned a new identification number.

Repeating laboratory testing during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol. Herein, study intervention is defined as abiraterone plus prednisone/prednisolone and blinded study drug abemaciclib/placebo.

6.1. Study Intervention(s) Administered

All participants will receive therapy with abiraterone CCI [redacted] plus prednisone CCI [redacted] Prednisolone may be used in lieu of prednisone per local abiraterone prescribing information or where prednisone is not commercially available. In this protocol, prednisone implies prednisone or prednisolone.

Blinded study drug (abemaciclib or placebo) will be administered at a starting dose of CCI [redacted] at approximately the same time every day. Placebo will be provided as a tablet formulation and will be matched in size, color, and shape to abemaciclib tablets to maintain the study blind.

Blinded study drug should be swallowed whole with a glass of water (do not chew, crush, split, dissolve in water, or alter in any way prior to swallowing). Blinded study drug may be taken with or without food.

If a participant misses a dose at the scheduled time for nonmedical reasons, the dose should be taken as soon as possible on the same day CCI [redacted] If a participant vomits after taking a dose, then the dose should not be retaken, and the next dose should be taken at the usual scheduled time. Instruct patients not to ingest tablets if broken, cracked or otherwise not intact.

The investigator or his/her designee is responsible for the following:

- Following the protocol at all times.
- Explaining the correct use of the drugs and planned duration of each individual's treatment to the participant/study-site personnel/legal representative.
- Verifying instructions are followed properly.
- Maintaining accurate records of blinded study drug dispensing and collection.
- At the end of the study, returning all unused blinded study drug to Lilly, or its designee, unless the site agrees and is authorized by Lilly or its designee to destroy unused medication, as outlined in the Pharmacy Manual.

This table provides details on the interventions used in this clinical study.

Intervention Name	Abemaciclib	Matching Placebo	Abiraterone	Prednisone
Authorized as defined by EU Clinical Trial Regulation	CCI			
Dosage Level(s)				
Route of Administration	Oral	Oral	Oral	Oral

Abbreviation: NA = not applicable.

6.1.1. Packaging and Labeling

Abemaciclib and matching placebo will be supplied by Lilly as tablets for oral administration. Abiraterone and prednisone will be sourced in accordance to local regulation and country requirements. Sites should confirm abiraterone and prednisone source to ensure adequate supply. All study intervention will be supplied in accordance with current Good Manufacturing Practice and labeled according to the country's regulatory requirements.

6.1.2. Background Therapy or Standard-of-Care

Participants who have not undergone bilateral orchiectomy are required to continue background ADT with an LHRH agonist/antagonist throughout the study. The choice of LHRH agonist/antagonist will be physician's choice. LHRH agonist/antagonist dosing and administration will be in accordance with the prescribing information.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained for blinded study drug and any discrepancies are reported and resolved prior to dispensing.

Only participants randomized in the study may receive study intervention. All study intervention should be stored according to their associated product label and taken as indicated. Blinded study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

Only authorized study personnel may supply blinded study drug. The investigator or authorized study personnel are responsible for blinded study drug accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused blinded study drug are provided in the Pharmacy Manual.

6.2.1. Selection and Timing of Doses

The first dose of abiraterone plus prednisone and abemaciclib/placebo should be initiated within 7 days following randomization. A treatment cycle is defined as an interval of 28 days (±3 days).

Abiraterone and prednisone should be administered orally once daily, according to the respective prescribing information.

Abemaciclib/placebo will be administered orally CCI at approximately the same times each day. Details on treatment administration are described in Section 6.1. In the event of a dose suspension due to toxicity immediately prior to the beginning of a cycle, the PK sampling schedule outlined in Section 1.3.1 may require adjustment and the sponsor should be notified.

A delay or an earlier start of a cycle due to logistical reasons (for example, due to holiday or vacation, weekend, inclement weather, or other unforeseen circumstances), will be permitted for up to a maximum of 7 days (and not be considered a protocol violation). During this period, if the participant has adequate drug supply, he may continue study intervention per investigator's discretion; additional blinded study drug may be dispensed at the investigator's discretion. Reasons for additional dispensing must be documented.

Participants may continue to receive study intervention with abiraterone, prednisone and abemaciclib/placebo until evidence of disease progression, or any discontinuation criteria are met (See Section 7).

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants who meet all eligibility criteria (Section 5) will be randomly assigned to receive abiraterone plus prednisone in combination with abemaciclib or placebo.

The IWRS will use randomization stratification factors (Section 4.1) to assign double-blind study drug (abemaciclib or placebo) to each patient. Before the study is initiated, log in information and instructions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA (Section 1.3).

6.3.1. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is completed. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly's data and statistical warehouse. Any changes to this unblinding plan may be described in a protocol amendment, the SAP, and/or a separate unblinding plan document.

Efficacy information will not be shared with sites until the study is completed. Upon study completion (see Section 4.4), investigators may unblind patients to study treatment assignment.

Unblinding of the investigator and the patient at the time of documented objective disease progression is permitted to ensure optimal patient management and/or facilitate selection of

subsequent treatment. The investigator must consult with the Lilly CRP/CRS prior to unblinding. Unblinding must be performed through the IWRS.

If an investigator or participant is unblinded, the participant must be discontinued from the study intervention and will undergo post-discontinuation follow-up. Long-term follow-up procedures will be followed until death, loss of follow-up, withdrawal of consent, or study completion.

6.3.2. Unblinding at Interim Analyses

See Section 9.5 for details on the conduct of interim analyses. Only the independent DMC is authorized to evaluate unblinded futility and interim efficacy analyses. The DMC will be independent and consist of at least 3 members external to Lilly, none of whom are involved as study investigators, including at least 1 clinician and 1 statistician. The DMC will communicate any recommendations based on the interim analyses to the Lilly Senior Management Designee. Further details are included in the DMC Charter. For those analyses assigned to the DMC, only the designated Statistical Analysis Center, which is independent of the sponsor, will perform analyses on unblinded data. Study sites will receive information about interim results only if they need to know for the safety of their patients. Further details are included in the study unblinding plan.

6.3.3. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should contact the Lilly CRP/CRS prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the patient. If a participant's treatment assignment is unblinded, Lilly must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. This option must be used when the participant's acute well-being requires knowledge of the participant's treatment assignment.

All calls resulting in an unblinding event are recorded and reported by the IWRS. If the investigator or participant becomes unblinded, that participant will be discontinued from study intervention and will undergo post-discontinuation follow-up. Long-term follow-up procedures will be followed until death, loss of follow-up, or withdrawal of consent, or study completion.

6.3.4. Inadvertent Unblinding

Every effort will be made to blind both the participant and the investigator to the identity of the blinded study drug, but the inadvertent unblinding of a participant may occur. If an investigator, site personnel, or participant is inadvertently unblinded, the unblinding will not be sufficient cause for the participant to be discontinued from study intervention or excluded from study analyses.

In cases in which there are ethical reasons for the participant to remain on the study intervention in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP/CRS for the participant to continue in the study.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each cycle.

Compliance with blinded study drug will be assessed by counting returned tablets. Compliance with abiraterone and prednisone will be assessed by participant's interview. Study intervention administration data will be recorded in the participant's medical record and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

Participants who are significantly noncompliant may be considered for discontinuation from study intervention after discussion with Lilly CRP/CRS. A participant may be considered significantly noncompliant if he misses more than 25% of the prescribed dosage in a given cycle. Similarly, a participant may be considered significantly noncompliant if he is judged by the investigator to have intentionally or repeatedly taken more than (≥125%) of the prescribed amount of medication. Dose suspensions or delays related to toxicity may occur and will not result in a participant being considered noncompliant.

6.5. Dose Modification

Dose adjustments (suspensions and reductions) will be made based on the clinical assessment of hematologic and nonhematologic toxicities (defined as an AE possibly related to study intervention per investigator judgment). The CTCAE v5.0 will be used to assess AEs. Study intervention may be suspended for a maximum of 28 days to allow a patient sufficient time for recovery from treatment-emergent AEs. If a participant does not recover from the toxicity within 28 days from the date of dose suspension, the participant should be considered for permanent discontinuation from study intervention. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the Lilly CRP/CRS.

If either abiraterone/prednisone or abemaciclib/placebo has been discontinued or maximally dose reduced due to toxicity and the toxicity has not resolved, patients may continue to receive the other interventions at the current dose if it is apparent that the toxicity is not related to these other interventions and the patient continues to receive clinical benefit.

Dose reductions for blinded study drug should be performed as shown in the table below. Abemaciclib/placebo must be reduced sequentially by 1 dose level unless an exception is granted in consultation with the Lilly CRP/CRS. Mid-cycle dose reductions for abemaciclib/placebo may be implemented by informing patients to reduce the number CCI [redacted]

6.5.1. Dose Reductions for Blinded Study Drug (Abemaciclib/Placebo

Study Drug	Starting dose	Dose Reduction			
		First	Second	Third	Fourth
Abemaciclib/ Placebo	CCI [redacted]				

Abbreviations: CCI [redacted] mg = milligrams.

Dose adjustments for abiraterone and prednisone should follow prescribing information. See Section 6.5.3 for guidance on dose modification for abnormal liver function test.

For participants requiring a dose reduction of any study intervention, re-escalation to a prior dose level is permitted only after consultation with and approval by the Lilly CRP/CRS.

6.5.2. Dose Modifications - Abemaciclib/Placebo

The table below provides a guidance for the management of treatment-emergent, related, and clinically significant AEs of abemaciclib/placebo. An investigator may suspend or reduce doses without meeting one of the criteria below and would not be considered a protocol deviation.

Participants undergoing surgical procedures should follow the guidelines below:

- For minor surgeries and procedures (for example, ambulatory), investigators should treat as clinically indicated and closely monitor any signs of infection or healing complications.
- For major surgeries, the recommendation is to suspend dosing of abemaciclib/placebo for at least 7 days before surgery and may be resumed as clinically indicated.
- Consider monitoring neutrophils and platelets before surgery and before resuming abemaciclib/placebo. The scars should be aseptic and healing process be reasonable before resuming abemaciclib/placebo.

Toxicity Dose Modifications of Abemaciclib/Placebo

Abbreviations: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017).

Note: Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the first event. As a general guidance, based on the risk/benefit balance assessment per the investigator, for a participant who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of the same Grade 3 hematological toxicity, the investigator may consider resuming the participant on the same dose should the participant satisfy the following conditions:

- The participant showed stable hematological counts (≤Grade 2) during that timeframe
- In the absence of any infectious sign or risk factor
- The participant is benefiting from study intervention.

6.5.3. Dose Modifications for Increased ALT or AST - Abemaciclib/Placebo and Abiraterone

Measure serum aminotransferases (ALT and AST) and bilirubin levels prior to starting study intervention and every 2 weeks for the first 3 months, and monthly thereafter.

After Cycle 14, patients eligible for remote telehealth visits will have laboratory assessments every 2 months, unless more frequent assessment is deemed necessary per investigator judgment. During telehealth visits, ALT, AST and bilirubin monitoring may be performed locally per investigator discretion in accordance with the abiraterone prescribing information. See SoA (Section 1.3) for details.

Promptly measure ALT, AST, ALP, TBL, DBL, GGT, and CK if clinical symptoms or signs suggestive of hepatotoxicity develop.

Review concomitant medications that are potentially hepatotoxic if patients develop liver function test abnormalities.

The table below provides guidance for management of elevation of ALT or AST. An investigator may suspend or reduce doses without 1 of the below criteria being met. This would not be considered a protocol deviation.

Toxicity Dose Modifications for Increased ALT or AST - Abemaciclib/Placebo and Abiraterone

CTCAE Grade (See Section 10.10 [Appendix 10] for CTCAE 5.0 grading of ALT/AST)	Dose Modification
Grade 1 or Grade 2	No dose modification is required.
Persistent or recurrent Grade 2	Suspend abemaciclib/placebo and abiraterone until toxicity resolves to baseline or Grade 1. Resume abemaciclib/placebo at next lower dose. Resume abiraterone at current dose.
Grade 3	Suspend abemaciclib/placebo and abiraterone until toxicity resolves to baseline or Grade 1. Resume abemaciclib/placebo at next lower dose. Resume abiraterone at next lower dose[a].
≥Grade 2 with total bilirubin >2×ULN, in the absence of cholestasis or recurrent Grade 3[b] or Grade 4	Permanently discontinue abemaciclib/placebo and abiraterone.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP/CRS = Clinical Research Physician/Clinical Research Scientist; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ULN = upper limit of normal.

- Determination of persistent events will be at the discretion of the investigator.
- Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the restarting date of the study drug).

[a] If at any time, a patient develops a Grade ≥3 elevation of ALT or AST at the reduced dose of 500 mg once daily, permanently discontinue abiraterone.

[b] If recurrent Grade 3 (that is, within 8 weeks as measured from the restarting date of the study drug) is only observed for AST, the investigator may consult with the Lilly CRP/CRS prior to permanently discontinuing study intervention.

Hepatic monitoring should be initiated for patients who develop liver function test abnormalities. Refer to Section 8.2.2 for Hepatic Safety Monitoring.

CCI [redacted]

Additional safety data should be collected for patients who develop liver function test abnormalities. Refer to Section 8.2.2.1 for Additional Hepatic Safety Data Collection.

6.6. Continued Access to Study Intervention after the End of the Study

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks. Placebo will no longer be administered.

The continued access period will apply to this study only if at least 1 participant is still on study intervention when study completion occurs. Lilly will notify investigators when the continued access period begins.

Participants are not required to sign a new ICF before treatment is provided during the continued access period; the initial ICF for this study includes continued access under this protocol.

Participants will be discontinued from study intervention in the following circumstances:

- clinical or radiographic disease progression
- the investigator determines it is in the participant's best interest to discontinue the study intervention
- the participant requests to discontinue the study intervention
- unacceptable toxicity
- initiation of a new anticancer therapy; discontinuation of the study intervention will occur prior to the introduction of the new therapy, and
- the participant is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Continued access follow-up will begin when the participant and the investigator agree to discontinue study intervention and lasts approximately 30 days. Follow-up procedures will be performed as shown in the Continued Access SoA (Section 1.3.2).

Participants who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Participants who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

6.7. Treatment of Overdose

In case of overdose, use supportive therapy. There is no known antidote for abemaciclib overdose. In case of overdose, the patient should receive supportive measures. Refer to the specific IB and/or Product Label for the applicable targeted agent(s) with marketed approval.

In the event of an overdose, the investigator should:

- Contact the Lilly CRP/CRS immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.

- Obtain a plasma sample for PK analysis as soon as possible after the overdose has been identified, unless the Lilly CRP/CRS specifies otherwise.
- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Lilly CRP/CRS based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications including over-the-counter and analgesics use must be recorded in the CRF. Concomitant medications and supportive care therapies must also be documented at time of discontinuations and at the short-term 30-day follow-up visit. The Lilly CRP/CRS should be contacted if there are any questions regarding concomitant or prior therapy.

Permitted:

Bone loss prevention treatments (for example, bisphosphonates or denosumab) per their respective approved labels. Initiation of and switching between bone loss prevention treatments is permitted during study if it is in the absence of disease progression, and due to reasons including, but not limited to, tolerability.

In the absence of radiographic progression:

- one course of palliative radiotherapy at a single site of bone metastases present at baseline is permitted provided medical management, such as with analgesics, is insufficient.
- one surgical intervention for symptomatic bone metastases or the prevention of a skeletal-related event, such as an impeding fracture, is permitted at a single site of bone metastases present at baseline.
- surgery/palliative radiotherapy for urinary tract symptoms are permitted.

Abemaciclib/placebo should be suspended to allow for correction of possible ongoing relevant study drug related adverse events (neutropenia/thrombocytopenia/anemia), before a participant undergoes palliative radiation treatment, and may be restarted after 2 weeks as long as any bone marrow toxicity has recovered.

Abemaciclib/placebo should be suspended before elective surgery to allow for correction of possible ongoing relevant study drug related adverse events (neutropenia/thrombocytopenia/anemia), and prior to urgent interventions. Abemaciclib/placebo may be resumed as clinically indicated. Closely monitor any signs of infection or healing complications. The incisions should be aseptic and healing process reasonable before resuming abemaciclib/placebo.

Refer to the prescribing information for abiraterone and prednisone.

All palliative radiotherapy and surgery procedures must be documented in the CRF.

Prohibited:

No other anticancer therapy except that required by the protocol will be permitted while participants are on study intervention (including, but not limited to anti-hormonal agents, other

CDK4 and/or CDK6 inhibitors, biologics, other antineoplastic and investigational agents, chemotherapy, radiopharmaceuticals, immunotherapy, anticancer vaccines, ketoconazole).

Drugs, or herbal/non-herbal products (for example, saw palmetto or pomegranate) that have known prostate cancer activity and/or are known to affect PSA levels, are not permitted while on study intervention. Spironolactone is not permitted. Megestrol acetate as an appetite stimulant is not permitted.

Drug-Drug Interaction:

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies:

- coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (area under the concentration-versus-time curve [AUC]) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE), and
- coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF).

Strong inhibitors of CYP3A (given via non-topical routes of administration) should be substituted or avoided if possible (Section 10.7, Appendix 7). This includes grapefruit or grapefruit juice. Avoid oral administration of the very strong CYP3A inhibitor, ketoconazole.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of abemaciclib/placebo by CCI at the start of CYP3A inhibitor treatment. That is, for patients receiving CCI reduce the dose to CCI For patients who have already dose reduced to CCI for tolerability, reduce the dose further to CCI respectively. Alternatively, the investigator may consider suspending abemaciclib/placebo for the duration of the CYP3A inhibitor medication. Dose suspensions ≥28 days must be discussed with Lilly CRP/CRS.

Upon discontinuation of the strong CYP3A inhibitor, abemaciclib/placebo may be resumed at the same dose level or re-escalated to the dose that was used before starting the strong inhibitor after a sufficient washout period (at least 3 half-lives of the strong inhibitor). Re-escalation of the abemaciclib/placebo dose requires review and approval from Lilly CRP/CRS.

Inducers of CYP3A should be substituted or avoided if possible (Section 10.7, Appendix 7). Coadministration with a CYP3A inducer ≥28 days must be discussed with Lilly CRP/CRS.

Abiraterone is a substrate of CYP3A4, and as such it is recommended to avoid concomitant strong CYP3A4 inducers. Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. For further information regarding the potential for abiraterone and/or prednisone to affect the exposures of other medicinal products, or for the potential for medicinal products to affect the exposures of abiraterone and/or prednisone refer to prescribing information.

Transporter Substrates:

At clinically relevant concentrations, abemaciclib inhibits the transporters P-glycoprotein, breast cancer resistance protein, organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. The observed serum creatinine increase in clinical studies

with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K. In vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin and dabigatran, may occur.

Vaccines:

Live vaccines should be avoided during, and up to 90 days after the last dose of study treatment.

6.8.1. Supportive Care

Patients should receive supportive care to maximize quality of life as judged appropriated by the treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP/CRS. Use of all supportive care therapy and concomitant medications should be captured in the CRFs.

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria. Granulocyte colony-stimulating factor (G-CSF) or similar agents are not permitted as primary prophylaxis.

The use of G-CSF is permitted at the discretion of the investigator based on American Society of Clinical Oncology (ASCO; Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2009) guidelines. If the administration of growth factors is clinically indicated, dosing of abemaciclib/placebo must be suspended and must not be recommenced within 48 hours of the last dose of growth factors being administered. The dose of abemaciclib/placebo must be reduced by 1 dose level following the administration of growth factors.

Transfusion therapy is permitted during the study if clinically indicated at any time during the study but should not be administered to enable a patient to satisfy study inclusion criteria.

Erythropoiesis-stimulating agents (ESAs; including erythropoietin and darbepoetin) may be used in accordance with the ASCO/ASH guidelines (Rizzo et al. 2010).

6.8.2. Supportive Management for Diarrhea

When study intervention is initiated, the participants should receive instructions for the management of diarrhea. In the event of diarrhea, supportive measures should be initiated **as early as possible**. These include:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear fluids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to either baseline or Grade 1, blinded study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When blinded study drug recommences, dosing should be adjusted as outlined in Section 6.5.2.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, antibiotics should be considered.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluid (IV hydration) and electrolyte replacement.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study are handled as part of Section 10.1.9, Appendix 1.

7.1. Discontinuation of Study Intervention

Discontinuation of study intervention (abiraterone, prednisone/prednisolone, and blinded study drug abemaciclib/placebo) does not constitute withdrawal from the study.

Participants who discontinue study intervention should remain in the study and be followed for primary, secondary, and exploratory endpoints.

Following discontinuation of study intervention, participants will enter the short- and long-term follow-up periods and scheduled assessments should continue according to the SoA (see Section 1.3) until death, loss of follow-up, or withdrawal of consent.

Participants with PSA-only progression should continue study intervention where participant safety is not compromised. Although PSA measurements will be performed in this study, progression or change in PSA values should not be used as the sole criterion for determining disease progression or discontinuation of study intervention.

Participants will be discontinued from study intervention in the following circumstances:

- unacceptable toxicity
- radiographic progression as described in Section 8.1
- initiation of a new anticancer therapy. Discontinuation of the study intervention will occur prior to the introduction of the new therapy.
- the participant is significantly noncompliant with study procedures and/or intervention
- the investigator determines it is in the participant's best interest to discontinue the study intervention the participant requests to discontinue the study intervention
- the participant's designee (legal representative) requests that the participant discontinues the study intervention
- the participant is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

The reason and date of discontinuation will be collected for all participants.

In the absence of radiographic progression, imaging (CT/MRI and bone scans) must be performed within 14 days of discontinuation due to symptomatic progression unless prior scans were performed ≤14 days prior to symptomatic progression.

In exceptional circumstances, a participant may continue study intervention beyond radiographic progression if there is no effective alternative therapy and/or the participant, in the opinion of the

investigator, is receiving clinical benefit from the study drug. In these rare cases, the investigator must obtain documented approval from the Lilly CRP/CRS to allow the participant to continue study intervention. Additionally, the participant must reconsent prior to continuing to receive study intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant will be discontinued from the study in the following circumstances:

- at any time at the participant's own request.
- at the request of the participant's designee (for example, parents or legal guardian).
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

At the time of discontinuing from the study, a follow-up safety visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Randomized Patients

The criteria for enrollment must be followed explicitly. If the investigator or site identifies a patient who did not meet enrollment criteria and who was inadvertently randomized, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently randomized, the investigator site will be notified. Patients who are inadvertently randomized should be discontinued from the study and will have follow-up procedures performed as shown in the SoA (Section 1.3).

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those

who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up. Lilly personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

Study procedures and their timing are outlined in the SoA (Section 1.3).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Appendix 2 (Section 10.2) provides a list of laboratory tests that will be performed for this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

Tumor and symptomatic progression will be assessed for each participant according to the SoA (Section 1.3). During study, unscheduled tumor assessment and appropriate imaging should be considered if there are signs or symptoms suggestive of disease progression.

For all patients, imaging (CT or MRI of the chest, abdomen, and pelvis and radionuclide bone scan) will be performed at screening and repeated every 12 weeks for the first 24 weeks and every 16 weeks thereafter, according to calendar days from start of study therapy (C1D1), regardless of treatment delays per the SoA (Section 1.3). Imaging should be performed within 7 days prior to the scheduled assessment.

Imaging should be performed within 14 days of discontinuation from study intervention due to symptomatic progression in the absence of documented radiographic progression (unless prior scans were performed ≤14 days).

The method of assessment used at baseline must be used consistently for serial tumor assessment throughout the study.

All CT/MRI and bone scans will be collected and stored centrally for BICR. Any pre-baseline scans documenting metastatic disease (including PSMA-PET/CT scans) will be collected and stored centrally for BICR. In exceptional cases, when pre-baseline scans are not able to be collected from an outside institution, the corresponding radiology reports are acceptable and will not be considered a protocol violation. Refer to imaging manual for additional details.

The primary efficacy endpoint is rPFS assessed by the investigator.

Radiographic progression-free survival (rPFS) will be assessed by sequential imaging studies and is defined as the time from the date of randomization to the earliest date of investigator-assessed radiographic disease progression in soft tissue (per RECIST 1.1) AND/OR bone disease (per the below criteria adapted from PCWG3), or death from any cause, whichever occurs first.

Soft tissue disease will be assessed per RECIST 1.1, see Section 10.9, Appendix 9. Radiographic disease progression in soft tissue does not require a confirmatory scan.

Bone lesions will be assessed by bone scintigraphy (bone scans). Positive hot spots on the bone scan should be considered unequivocal sites of malignant disease to be recorded as metastatic bone lesions. Changes in intensity of uptake alone do not constitute either progression or regression.

Bone progression is defined as:

- **Progression at the Week 13 scan:**
  Appearance of ≥2 new lesions on the Week 13 scan **compared to baseline scan** AND ≥2 additional new lesions on a confirmatory scan performed ≥6 weeks later or on the next scheduled scan (Week 25 scan).
  A total of ≥4 new lesions compared to baseline; this is the "2+2 rule".
  The date of progression is the date of the scan that documents the first 2 new lesions.

- **Progression at the Week 25 scan or later:**
  CCI [redacted]

Protocol-specified documentation for radiographic progression

Date Progression Detected	Criteria for Progression	Criteria for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Bone Progression			
Week 13	≥2 new lesions compared to baseline bone scan.	Requires confirmation on a scan performed ≥6 weeks later or on the next scheduled scan (Week 25 scan).	Confirmatory scan must show ≥2 additional new lesions compared to the Week 13 scan.
Week 25 or later	CCI [redacted]		
Note: Progression detected at an unscheduled bone scan prior to Week 25 will require the same criteria for documentation of disease progression as Week 13 with a confirmatory scan ≥6 weeks later or at the next scheduled scan.			
Soft Tissue Progression			
Any post-baseline scan	Progressive disease on CT or MRI per RECIST v1.1.	No confirmatory scan required.	Not applicable.

In addition to the primary endpoint of rPFS by investigator-assessed radiographic disease progression or death, rPFS by BICR will be assessed. A central radiology vendor will collect and store images for BICR review. Secondary efficacy endpoints include clinical progression-free survival (cPFS), castration-resistant prostate cancer (CRPC)-free survival, time to PSA progression, time to initiation of new anticancer therapy, time to symptomatic progression and OS.

See Sections 9.4.3 and 9.4.4 for definitions of all secondary and exploratory efficacy endpoints.

8.2. Safety Assessments

Planned time points for all safety assessments (for example, vital signs and laboratory tests) are provided in the SoA (Section 1.3).

Results from any clinical laboratory test analyzed by a central laboratory (refer to Section 10.2, Appendix 2) will be provided to investigative sites by Lilly or its designee.

8.2.1. Clinical Safety Laboratory Tests

See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be worsened by study intervention.

All laboratory tests with abnormal values considered clinically significant and possibly related to study intervention during study intervention until the completion of V801 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly CRP/CRS.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2, must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and the laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.2. Hepatic Safety Monitoring

Close hepatic monitoring and evaluation

Liver testing (Section 10.5, Appendix 5), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5× ULN	ALT or AST ≥5× ULN or ALT or AST ≥3× ULN concurrent with TBL ≥2× ULN
ALT or AST ≥1.5× ULN	ALT or AST ≥3× baseline or ALT or AST ≥2× baseline concurrent with TBL ≥2× ULN

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly CRP/CRS. At a minimum, evaluation should include physical examination, a thorough medical history that includes symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal, and dietary supplements), and history of alcohol drinking and/or other substance abuse. In addition, the evaluation should include a blood test for PT-INR; serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial evaluation results, further testing should be considered, in consultation with the Lilly CRP/CRS, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, and/or a liver biopsy.

For patients who experienced hepatoxicity and resumed treatment, AST, ALT, and bilirubin should be monitoring every week for the first month, every 2 weeks for the following 2 months and monthly thereafter.

8.2.2.1. Additional Hepatic Safety Data Collection

Additional safety data should be collected via the CRF if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT or AST <1.5× ULN

- Elevation of serum ALT or AST to ≥5× ULN on 2 or more consecutive blood tests.
- The combination of elevated ALT or AST ≥3× ULN and elevated TBL ≥2× ULN.

In participants enrolled with baseline ALT or AST ≥1.5× ULN

- Elevated ALT or AST ≥3× baseline on 2 or more consecutive tests.
- The combination of elevated ALT or AST ≥2× baseline and elevated TBL ≥2× ULN.

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests.
- Occurrence of a hepatic event considered to be an SAE.

8.2.3. Guidance for Monitoring Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen, cystatin C, or calculated glomerular filtration rate based on cystatin C.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. Other measures of renal function, such as cystatin C, or GFR, should be used as an alternative to either creatinine or creatinine calculations of GFR. A serum cystatin C is collected with central chemistry laboratory sample. If deterioration of renal function is suspected per the investigator's clinical assessment, and considered possibly related to blinded study drug, dose alteration should follow the protocol guidance for non-hematological toxicities in Section 6.5.2.

8.2.4. Guidance for Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an ADR for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2, with serious cases and fatal events reported. Additional information is available in the IB.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis such as hypoxia, dyspnea, cough, and fever, and investigate and treat as per local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high-resolution CT, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Section 6.5 for guidance on dose adjustments of abemaciclib/placebo for participants with ILD/pneumonitis. Discontinue abemaciclib/placebo in cases of severe (Grade 3 or Grade 4) ILD/pneumonitis.

8.2.5. Guidance for Venous Thromboembolic Events (VTEs)

In breast cancer, VTE has been identified as an ADR for abemaciclib in combination with ET. In the randomized Phase 3 studies in participants with breast cancer who received abemaciclib in combination with ET, a greater number of participants experienced VTEs in the abemaciclib plus ET arms than in the placebo plus ET arm or ET alone arm. The majority of participants who experienced VTEs were treated with anticoagulants.

In studies with single-agent abemaciclib use in the metastatic breast cancer population or other tumor types, including non-small cell lung cancer, no increased rates of VTEs were observed as compared to the incidence of VTEs for these patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known.

Monitor participants for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate. Dose modifications and management of abemaciclib/placebo should follow the protocol guidance for VTE in Section 6.5.2.

8.2.6. Guidance for Hypertension, Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions Due to Mineralocorticoid Excess

Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition.

Monitor patients for hypertension, hypokalemia, and symptoms of fluid retention at least once a month. Patients with low potassium while on study or a history of hypokalemia from a preexisting or concurrent medical condition should be considered for more frequent laboratory electrolyte evaluation per investigator's discretion. Control hypertension and correct hypokalemia before and during treatment.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking abiraterone. The safety of abiraterone in patients with left ventricular ejection fraction <50% has not been established.

Refer to abiraterone prescribing information.

8.2.7. Guidance for Adrenocortical Insufficiency

Adrenocortical insufficiency was reported in patients receiving abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.

Monitor patients 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. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Refer to abiraterone prescribing information.

8.2.8. Guidance for Hypoglycemia

Severe hypoglycemia has been reported when abiraterone was administered to patients with preexisting diabetes receiving medications containing thiazolidinediones (including pioglitazone) or repaglinide. Monitor blood glucose in patients with diabetes during and after discontinuation of treatment with abiraterone. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Refer to abiraterone prescribing information.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

Lilly standards for reporting AEs are to be followed regardless of country regulatory requirements are less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, irrespective if the AE is related to study intervention.

The definitions of the following events can be found in Section 10.3, Appendix 3:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

The investigator will use CTCAE version 5.0 (NCI 2017) to assign AE severity grades.

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3, Appendix 3.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via CRF/electronic data entry/designated data transmission methods the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

In addition, study site personnel will record via CRF/electronic data entry/designated data transmission methods any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study intervention via CRF/electronic data entry/designated data transmission methods.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study intervention or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the study intervention and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via CRF/electronic data entry/designated data transmission methods, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

8.3.1. Timing and Mechanism for Collecting Events

All SAEs will be collected from the signing of the ICF until participation in study has ended.

All AEs will be collected from the signing of the ICF until the short-term 30-day follow-up visit.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF. Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving abemaciclib, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3, Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation (the participant summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Also see Timing and Mechanism for Collecting Events table in Section 10.6, Appendix 6.

8.3.2. Method of Detecting AE and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3, Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require intervention to prevent one of the other outcomes listed in the definition above.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the participant's medical history at the time of enrollment should not be considered SAEs.

Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study intervention or other protocol-required procedure) should not be considered SAEs.

Pregnancy (during maternal or paternal exposure to study intervention) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus. See Section 8.3.5 for details.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions are serious events that are not listed in the IB and that the investigator identifies as related to study intervention or study procedure. United States 21 CFR 312.32 and Regulation (EU) No 536/2014 and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidance.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution to baseline, stabilization, the event is otherwise explained, or the participant dies or is lost to follow-up (as defined in

Section 7.3). Further information on follow-up procedures is provided in Section 10.3, Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will
    - Attempt to obtain a consent to release information from the pregnant female partner directly, and
    - If consent is granted, within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

  If consent is not obtained, the investigator will document refusal of consent or the reason that the consent was not obtained.

  If consent is obtained, the female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for abemaciclib include neutropenia, infections, diarrhea, hepatic events including increases in AST/ALT, VTE, and ILD/pneumonitis. No AEs need to be adjudicated. Section 6.5 presents the dose modification guidelines.

8.4. Pharmacokinetics

Pharmacokinetic samples will be collected from study participants at the visits and times specified in the SoA (Section 1.3.1). At all PK timepoints, a volumetric absorptive microsampling device will be used to collect a blood sample by capillary puncture. In addition, on Cycle 1 Day 1 and Cycle 3 Day 1, a PK sample will also be collected at approximately the same time (within [+/-] 10 minutes) as the blood microsample via venous puncture collection into a vacutainer. It is important to collect accurate information for the time and date of each PK sample on the lab requisition form.

It is also important to collection accurate information for the time and date of doses of blinded study drug around the PK sampling collection times. Accordingly, during the PK sampling period (Cycle 1 Day 1 to Cycle 3 Day 1), participants will complete a Patient Dosing Diary to record the time and date of blinded study drug doses, which will be utilized in PK assessments. The information in this diary should be collected and reviewed on Day 1 of Cycle 2 and Cycle 3 for each prior cycle and be documented in the CRF. This diary is not intended to monitor compliance.

Pharmacokinetic samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of abemaciclib and its metabolites, M2 and M20, will be determined using validated liquid chromatography with tandem mass spectrometry methods.

Pharmacokinetic samples may be retained for a maximum of 1 year following last participant visit for the study.

Additional samples may be collected during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A germline DNA sample that can be used for genetic research will originate from the whole-blood sample collected in Section 8.7.3 for biomarker research. Genetic research may include analysis of germline polymorphisms that are relevant to study intervention, mechanism of action, the variable pharmacokinetics and response to study drug(s) (including evaluation of AEs or differences in efficacy), cell cycle, immune function, and pathways associated with prostate cancer. Examples of genetic research include germline polymorphisms in genes leading to homologous recombination deficiency repair (for example, BRCA1, BRCA2, CHEK2, ATM,

MUTYH, APC, HOXB13, MSH2, TP53, PALB2, PMS2, MLH1, MSH2, MSH6), common germline polymorphisms in genes involved in the cell cycle (for example, CDKN1A, CDKN1B, and AURKA), common germline polymorphisms associated with immune variations in immune rejection of tumors (for example, CD28, ICOS, PDCD1, TNFSF4, CD226, HAVCR2, CTLA4, and LAG3), common germline polymorphisms in genes associated with increase in risk of prostate cancer (for example, MTHFR, some variants of HSD17, SLCO2, CYP17, CYP19, SRD5A2 and HSD3B1), and common germline polymorphisms in genes related to the mechanism of action of abemaciclib or anti-androgen therapy. Genetic analysis results may occur after the clinical study report is written and therefore a separate genetic Data Analysis Plan will be developed.

Genetic samples may be assessed by various methods, including whole-genome and exome sequencing, gene panel sequencing, genome-wide association studies, and DNA candidate gene studies. Regardless of the technology utilized, data generated will be used only for the specific genetic research scope described in this section, and within the limits of this protocol.

Genetic research may lead to the identification of genetic incidental findings. Genetic incidental findings are variations present in germline DNA that are discovered unintentionally and that may nonetheless be of medical value or utility to the physician and the patient. The methods used in this study to perform genetic research are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, subject to local regulations, no incidental findings will be reported to the patients participating in genetic research.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Additional analyses within the research scope described in this section may be conducted if it is hypothesized that this may help further understand the clinical data. Samples may also be used to develop related research methods or to validate diagnostic tools or assays, but only within the specific research scope described in this protocol. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to the study intervention or study interventions of this class, and/or to understand study disease or related conditions, within the scope described in this protocol.

Genetic samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the study site personnel. Long-term sample retention is outlined in Section 10.1.12 (Appendix 1). Technologies are expected to improve during the storage period and, therefore, cannot be specifically named. Regardless of the technology utilized, data generated will be used only for the specific genetic research scope described in this section, and within the limits of this protocol.

8.7. Biomarkers

This study will analyze biomarkers relevant to study intervention, mechanism of action, the variable response to study drug(s) (including evaluation of AEs or differences in efficacy), cell cycle, immune function, or pathways associated with prostate cancer. Samples collected will enable examination of these questions through the measurement of biomolecules, including DNA, RNA, proteins, lipids, and other circulating or cellular elements. Derivatives of samples (for example tumor images) can also be used to identify biomarkers of patient response or resistance. Except for the cases detailed in Sections 8.7.1 (ctDNA sequencing without patient-matched germline subtraction) and 8.7.2 (tumor DNA sequencing without patient-matched

germline subtraction), biomarker analyses will not produce interpretable results on germline DNA and therefore will not lead to the identification of genetic incidental findings as described in Section 8.6. Biomarker analyses using DNA as a substrate will generate interpretable information on tumor somatic variants, tumor somatic copy number changes and tumor somatic rearrangements. Biomarker analyses using RNA as substrate will avoid the identification of genetic variants and will focus on quantifying gene expression and reporting tumor somatic gene fusions and other tumor somatic rearrangements. Biomarker analysis results may occur after the clinical study report is written and therefore a separate biomarker Data Analysis Plan will be developed.

Samples for biomarker research will be collected from all participants as specified in the sampling schedule (Section 1.3.1), where local regulations allow. It is possible that biomarker data for participants in the study have already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.7.1 and 8.7.2.

Additional analyses within the specific research scope described in this section may be conducted if it is hypothesized that this may help further understand the clinical data. Samples may be used to develop related research methods or to validate diagnostic tools or assays, but only within the specific research scope described in this protocol. The samples may be analyzed as part of a multi-study assessment of non-genetic factors involved in the response to study intervention or study interventions of this class, and/or to understand study disease or related conditions, within the scope described in this protocol.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the study site personnel. Long-term sample retention is outlined in Section 10.1.12 (Appendix 1). Technologies are expected to improve during the storage period, and therefore, cannot be specifically named. Regardless of the technology utilized, data generated will be used only for the specific biomarker research scope described in this section, and within the limits of this protocol.

8.7.1. Plasma Samples for Biomarker Research

Plasma samples may be assessed by ELISA, microRNA profiling, metabolomics, and/or other relevant single-plex or multiplex-based assay methods for nongenetic factors that may predict for clinical benefit or correlate with treatment-related adverse events. Potential serum and plasma-based biomarkers to be investigated include, but are not limited to, antitumor antibodies, cytokines, chemokines, inflammatory factors, angiogenic biomarkers, and microRNAs.

Plasma samples may also be used for circulating tumor DNA (ctDNA) analyses. ctDNA analysis may be performed with patient-matched germline DNA subtraction. Germline DNA for each subject will originate from DNA extracted from whole blood as described in Section 8.7.3. Review of germline DNA sequencing results may be conducted, but only for data quality control purposes. At no point in this process will germline DNA variants be analyzed and interpreted by the research personnel. As such, ctDNA analysis with germline DNA subtraction will not produce interpretable results on germline DNA, is not considered genetic research, and therefore, will not lead to the identification of genetic incidental findings as described in Section 8.6.

ctDNA analysis may also be performed without germline DNA subtraction. In this case, it may be considered genetic research and the identification of genetic incidental findings is possible. Regardless of whether patient-matched germline DNA subtraction is used or not during ctDNA analysis, the methods used in this study for biomarker analyses are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, no incidental findings will be reported to the patients participating in biomarker research, subject to local regulations.

8.7.2. Tissue Samples for Biomarker Research

Archival tumor sample, obtained prior to initiating study treatment, will be collected, where available. The most recent sample is desired. Metastatic sample where available is preferred over primary tumor. Soft tissue as well as bony metastatic lesions are acceptable. The tumor samples will preferably be in the form of a formalin-fixed, paraffin embedded block. If this is not possible, approximately 20 slides of freshly prepared unstained 5-micron sections from the archival tumor block may be provided. Samples can be collected at any time during study if not collected at screening. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided.

Pathology reports accompanying tumor tissue will be requested where available. Pathology reports must be coded with the participant number. Personal identifiers, including the participant's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned by the sponsor. The sponsor has a right to retain a portion of the submitted tissue, and archival blocks may be returned to the study site, upon request.

An optional fresh metastatic biopsy (formalin fixed and paraffin embedded) may be taken at the time of on-study radiographic progression, prior to start of new anticancer therapy if the investigator deems this to be appropriate and safe. Biopsy of a progressing metastatic lesion is preferred whenever possible. Soft tissue as well as bony metastatic lesions will be considered acceptable. If patient discontinues study for reasons other than radiographic progression, the biopsy should be considered only if the patient has completed at least 4 cycles of study treatment.

Various non-genetic biomarkers with potential prognostic or predictive value for the treatment of prostate cancer with study intervention are currently under investigation and may be assessed in this study. These tumor tissue non-genetic biomarkers include, but are not limited to, cell-cycle pathway genes/proteins (for example, D-cyclin alterations, CCNE1/2, CDKN2A/B, RB1 loss of function, E2F1, CDK4, CDK6, CDK2, FOXM1), PI3K pathway (for example, PTEN loss, PIK3CA, AKT1), MAPK pathway (for example, KRAS, NRAS, NF1), FGFR pathway (for example, FGF genes, FGFR1/2/3), and MYC, RB1 and other target gene signatures. In addition, subpopulations of tumor, stromal, and immune cells and several mRNA expression signatures related to abemaciclib and ET mechanism of action or hallmarks of cancer may be studied. Tumor samples may also be used to further characterize the tumor-immune microenvironment, including, but not limited to, cell-cycle proteins, T-cell checkpoint receptors and ligands, and intratumoral immune cell subsets, including T-regulatory cells, myeloid-derived suppressor cells, macrophages, natural killer (NK) cells, and B cells.

Tumor samples may be retrospectively assessed for the expression of the biomarkers indicated above using a variety of methodologies inclusive of, but not limited to, IHC, tumor imaging, RNA Scope, mass spectrometry, qRT-PCR, mRNA expression by RNA sequencing or hybridization, and somatic DNA mutations by tumor whole-exome or panel DNA sequencing.

Tumor DNA analysis (whole-exome or panel DNA sequencing) may be performed with patient matched germline DNA subtraction. Germline DNA for each subject will originate from DNA extracted from whole blood as described in Section 8.7.3. Review of germline DNA sequencing results may be conducted, but only for data quality control purposes. At no point in this process will germline DNA variants be analyzed and interpreted by the research personnel. As such, tumor DNA analysis with germline DNA subtraction will not produce interpretable results on germline DNA, is not considered genetic research, and therefore, will not lead to the identification of genetic incidental findings as described in Section 8.6.

Tumor DNA analysis may also be performed without germline DNA subtraction. In this case, it may be considered genetic research and the identification of genetic incidental findings is possible. Regardless of whether patient-matched germline DNA subtraction is used or not during the tumor DNA analysis, the methods used in this study for biomarker analyses are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, no incidental findings will be reported to the patients participating in biomarker research, subject to local regulations.

Tumor RNA sequencing analyses quantitate tissue mRNA expression levels, report gene fusions, splice variants, and other somatic rearrangements, and do not detect germline variants. Therefore, these analyses are not considered genetic research and no genetic incidental findings as described in Section 8.6 will be identified.

8.7.3. Whole-Blood Sample for Biomarker Research

This sample may also be used for the extraction of DNA that allows patient-matched germline DNA subtraction during ctDNA (Section 8.7.1), and tumor DNA analysis from tissue (Section 8.7.2).

This whole-blood DNA sample will be used to obtain germline DNA that may also be utilized for genetic research as described in Section 8.6.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Medical Resource Utilization and Health Economics

8.9.1. Patient-Reported Outcomes

Patient-reported outcome measures will be administered by paper questionnaires to assess pain, HRQoL, and patient-reported adverse events/toxicity. There are 4 PRO questionnaires included in this study. They should be completed before significant interaction with site personnel and administered in the following order:

1. Brief Pain Inventory – Short Form (BPI-SF) Worst Pain Numeric Rating Scale (NRS)

2. Functional Assessment of Cancer Therapy – Prostate (FACT-P)
3. EuroQol 5 Dimension 5 Level (EQ-5D-5L)
4. Patient-Reported Outcome – Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

The PRO questionnaires will be administered in the language in which the patient is fluent or literate and administered according to the SoA (Section 1.3) in countries where the questionnaires have been translated into the native language of the region.

8.9.1.1. BPI-SF Worst Pain NRS

The Worst Pain NRS item extracted from the BPI-SF is a single-item, patient-reported, 11-point horizontal scale (Atkinson et al. 2010). The single question of this scale is obtained from question #3 of the BPI-SF (Chapman and Loeser 1989) and assesses the participant's pain in the last 24 hours. This scale is anchored at 0 to 10, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine".

To determine time to pain progression, analgesic medication use will be assessed along with the data from the Worst Pain NRS. Data on analgesic medication use will be recorded on the concomitant medication CRF. The use of pain medications from the previous visit should be reviewed with the patient at each subsequent visit. Information on new or stopped analgesics should be recorded. This information should be collected during the study and at the 30-day follow-up visit. Analgesics/opioids consumed by patients will be classified into categories according to the AQA. AQA will then be used to determine if changes in the worst pain assessment are attributable to increased or decreased analgesia (Chung et al. 2014).

8.9.1.2. FACT-P

The FACT-P is an established and validated patient-reported measure for assessing quality of life and cancer-specific symptoms in participants with prostate cancer (Esper et al. 1997; Cella et al. 2009). The FACT-P includes 27 core items from the FACT-G and 12 items on prostate cancer related symptoms. This 39-item questionnaire assesses the participants' quality of life and cancer symptoms over the past 7 days and consists of 5 subscales (physical, social/family, emotional, functional well-being, and prostate cancer subscale). Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). Each item is then combined to produce subscale scores, as well as total scores for the FACT-G (ranging from 0 to 108) and FACT-P (ranging from 0 to 156). Higher scores represent better quality of life (Cella et al. 1993; Cella et al. 2009).

The FACT-GP5, item no. 5 on the FACT-P, assesses overall side effect bother over the past 7 days (Pearman et al. 2018) in association with reported PRO-CTCAE items.

8.9.1.3. EQ-5D-5L

The EQ-5D-5L (EuroQol Research Foundation 2019) is a standardized 5-item self-administered instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L assesses 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using a 5-level of severity (no problem, slight, moderate, severe, or extreme

problem). In addition, the EQ Visual Analog Scale records current self-rated health state from 0 (the worst imaginable health) to 100 (the best imaginable health). The recall period is "today".

8.9.1.4. PRO-CTCAE

The PRO-CTCAE is a patient-reported outcome measurement system developed by the NCI to collect symptomatic AEs from cancer participants enrolled in clinical trials (Basch et al. 2014; Dueck et al. 2015; Bennett et al. 2016). The intent of using the PRO-CTCAE is to provide participants' perspectives of their AE experience and will not be used for AE reporting. The information from PRO-CTCAE are only used strictly to the study's exploratory objective. In addition, this information will not be reviewed by the sites to minimize bias.

The PRO-CTCAE item library (Version 1.0; NCI 2020) includes 78 symptomatic AEs and a total of 124 total items drawn from the CTCAE that measure participants' symptomatic toxicities over the past 7 days. PRO-CTCAE responses are scored from 0 to 4 (or 0/1 for absent/present). From this item library, 6 specific AEs (13 total items) were selected based on the most frequent participant-felt AEs reported in abemaciclib and/or abiraterone:

- nausea (FS)
- diarrhea (F)
- abdominal pain (FSI)
- swelling (FSI)
- fatigue (SI), and
- hot flashes (FS)

(F=frequency; S=severity; I=interference)

8.9.2. Health Care Resource Utilization

Health care resource utilization will be collected in the CRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will include:

- hospitalization (yes or no) and duration of hospitalization (admission and discharge dates).
- emergency room visits (yes and number of events, or no).

9. Statistical Considerations

The SAP will be finalized prior to unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analysis focusing on the primary endpoint.

9.1. Statistical Hypotheses

Treatment of participants with high-risk mHSPC with abemaciclib in combination with abiraterone plus prednisone will provide a clinically meaningful increase in rPFS over treatment with placebo and abiraterone plus prednisone.

9.2. Sample Size Determination

Approximately 900 participants will be randomized into the study using a 1:1 ratio. The primary endpoint is rPFS. CCI [redacted] Accounting for the planned futility and interim analyses, the desired power is achieved under these assumptions when the primary analysis is conducted after approximately CCI rPFS events have occurred in the ITT population.

9.3. Analyses Sets

Population	Description
Intent-to-Treat (ITT)	All randomized participants, regardless of whether they took any doses of study intervention, or if they took the correct treatment. Participants will be analyzed according to the treatment group as randomized and not by actual treatment received.
Safety	All randomized participants who received at least 1 dose of any study intervention. Participants will be analyzed according to the first dose of study intervention they actually received, regardless of the arm to which they were randomized.
Measurable disease population	All randomized patients who have measurable disease in soft tissue at baseline according to RECIST v1.1. This population will be used for efficacy analyses based on soft tissue tumor response related endpoints such as best overall response.
Pharmacokinetic (PK) analysis	All randomized participants who received at least 1 dose of study intervention and at least 1 postbaseline evaluable PK sample.
Biomarker population	The subset of patients from the ITT population from whom a valid assay result has been obtained.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of sponsor or its designee.

All tests of treatment effects will be conducted at a 1-sided alpha level of .025, unless otherwise stated, and all CIs will be given at a 2-sided 95% level.

Full details of the planned analyses will be documented in the SAP. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the SAP. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.4.2. Primary Endpoint/Estimand Analysis

The primary endpoint of CYCLONE 3 will be investigator-assessed rPFS. Radiographic progression-free survival is defined as the time from the date of randomization to the earliest date of investigator-assessed radiographic disease progression in soft tissue (per RECIST 1.1) AND/OR bone disease (per adapted PCWG3, as described in Section 8.1), or death from any cause, whichever occurs first. Patients who have neither progressed nor died will be censored at the date of their last radiographic tumor assessment (if available) or the date of randomization (if no post-baseline radiographic assessment is available). The detailed censoring rules are described in the SAP.

The overall type I error will be controlled at a 1-sided alpha level of 0.025. The primary analysis of rPFS will be performed on the ITT population and will use the log-rank test stratified by the randomization factors. There is 1 planned futility analysis, 1 planned efficacy interim analysis, and the primary outcome analysis of rPFS.

Within the analyses of rPFS CCI [redacted] The futility analysis is planned to take place after CCI [redacted] There are 2 planned efficacy analyses of rPFS. An interim analysis will be performed afte CCI [redacted] The cumulative 1-sided type I error rate of 0.025 will be maintained CCI [redacted]

Statistical Analysis Milestones

Milestone	rPFS	One-sided Boundary p-value for rPFS Efficacy
CCI		

Abbreviations: CCI

a CCI

b CCI

9.4.3. Secondary Endpoints Analyses

9.4.3.1. rPFS by Blinded, Independent, Central Review

An rPFS analysis based on blinded independent central review data will be conducted. A central radiology vendor will collect and store images for BICR review.

9.4.3.2. Clinical PFS (cPFS)

Clinical PFS is defined as the time from the date of randomization to the earliest date of investigator-assessed radiographic disease progression, symptomatic progression, or death from any cause, whichever occurs first.

9.4.3.3. Castration-Resistant Prostate Cancer (CRPC)-free Survival

CRPC-free survival is defined as the time from the date of randomization to the earliest date of castration resistance, as demonstrated by any of the following (whichever occurs earliest):

- Confirmed PSA progression (as described in Section 9.4.3.5) with serum testosterone ≤50 ng/dL (≤1.73 nmol/L)
- Investigator-assessed radiographic progression with serum testosterone ≤50 ng/dL (≤1.73 nmol/L)
- Death from any cause.

9.4.3.4. Time to Symptomatic Progression

Time to symptomatic progression is defined as the time from randomization to any of the following (whichever occurs earlier):

- Symptomatic skeletal event (SSE), defined as cancer-related symptomatic fracture, surgery or radiation to bone, or spinal cord compression.
- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anticancer therapy.
- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

9.4.3.5. Time to PSA Progression

Time to PSA progression is defined as the time from the date of randomization to the date of first observation of PSA progression. The PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir (or baseline value if baseline is the lowest on study), which is confirmed by a second value obtained 3 or more weeks later. Any post-baseline PSA measurements within 12 weeks since baseline will be ignored in determining PSA progression.

9.4.3.6. Time to Initiation of New Anticancer Therapy

Time to initiation of new anticancer therapy is defined as the time from randomization until the first initiation of a new anticancer therapy.

9.4.3.7. Overall Survival

Overall survival is defined as the time from randomization until death from any cause.

9.4.3.8. Time to Pain Progression

Time to pain progression (using the BPI-SF Worst Pain NRS score and AQA score) is defined as the time from randomization to any of the following (whichever occurs earlier):

- an increase from baseline of at least 2 points in Worst Pain NRS score at 2 consecutive assessments at least 3 weeks apart, with no decrease from baseline in opioid use
- initiation of opioid use or increase from baseline in opioid use.

Participants who do not satisfy any of the criteria above will be censored at the time of the last known assessment that showed an absence of pain progression.

Further details concerning analyses on secondary endpoints can be found in the SAP.

9.4.4. Exploratory Endpoints Analyses

9.4.5. Safety Analyses

All participants in the safety analysis set defined in Section 9.4 will be evaluated for safety and toxicity.

The most current version of the MedDRA® will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term (LLT) will be used in the treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC.

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study drug.
- serious adverse events, including possible relationship to study drug.
- adverse events leading to dose adjustments.
- discontinuations from study treatment due to adverse events or death.
- treatment-emergent abnormal changes in laboratory values.
- treatment-emergent abnormal changes in vital signs and ECGs.

Full safety analysis descriptions can be found in the SAP.

9.4.6. Other Analyses

9.4.6.1. Patient-Reported Outcomes and Health Care Resource Utilization

For each PRO instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments. Data will be separately summarized using descriptive statistics. Further details will be provided in the SAP for each PRO instrument, respectively.

Frequency counts of hospitalizations and emergency room visits will be reported descriptively for each treatment arm by cycle.

9.4.6.2. Pharmacokinetic and Exposure-Response Analyses

Pharmacokinetic analyses will be conducted on all participants who have received at least 1 dose of study intervention and have at least 1 evaluable PK sample.

Abemaciclib PK analyses may include, but are not limited to:

(1) Summary analyses of individual and/or mean concentrations of abemaciclib, M2, and M20, grouped by analyte, dose level, time point, etc.
(2) Comparison of time-matched plasma and microsampling PK samples.
(3) Population PK modeling analysis to evaluate population PK parameters and inter-individual PK variability.

Relationships between exposure and measures of efficacy and safety may be explored.

9.5. Interim Analysis

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants. Unblinding details are specified in a separate blinding and unblinding plan document.

9.5.1. Safety Interim Analysis

The DMC will monitor the overall safety of the study. The DMC members will review unblinded safety data at each interim analysis. If a significant safety signal is identified, the DMC may recommend a protocol amendment, termination of enrollment, and/or termination of study treatment. The recommendations of the DMC will be communicated to the sponsor SMD.

In the event that blinded safety monitoring by the study team uncovers an issue that needs to be addressed by unblinding at the treatment group level, members of the DMC can conduct additional analyses of the safety data. Additionally, unblinding of a limited number of the sponsor representatives external to the study team may be required for evaluation of selected SAEs for determination of regulatory reporting.

There will be no prespecified rules for stopping the trial due to safety concerns. The DMC will meet and review the overall data approximately every 6 months thereafter while patients remain in the on-study intervention periods. At the recommendation of the DMC, the frequency of safety interim analyses may be modified. See Section 10.1.5.1 for further details.

9.5.2. Efficacy Interim Analysis

One futility analysis and one efficacy interim analysis are planned, as described in Section 9.4.2. If the futility boundary is met at the futility analysis, the DMC should recommend that the study be stopped for futility.

The efficacy interim analysis will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. The DMC will be instructed to recommend to the SMD that the sponsor be unblinded if the analysis of rPFS reaches statistical significance as described in Section 9.4.2 and any additional criteria specified in the DMC charter are met. See the separate unblinding plan for details.

The sponsor does not intend to stop the study based on the interim analysis of efficacy and all patients will continue to follow-up for all study objectives until study close. Participants randomized to the control group will not be permitted to cross over to the experimental group, as this will confound the assessment of OS. If the DMC makes a recommendation counter to this at an interim analysis, for example, the DMC recommends crossing all participants over to the experimental treatment, regulatory agencies may be consulted before any action is taken. Additionally, patients will remain blinded for the duration of the study unless specific unblinding criteria are met.

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

The SAP will describe the planned interim analyses in greater detail.

The timing of dissemination of data summaries based on interim analyses is addressed in Section 10.1.6, Appendix 1.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
    - Applicable ICH GCP Guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
    - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or the participant's legally authorized representative, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The sponsor and research sites have processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach and are compliant with General Data Protection Regulation (GDPR) data privacy regulations and the European Clinical Trial Regulation (CTR) (Articles 56, 57, 58).

10.1.5. Committees Structure

10.1.5.1. Independent Data Monitoring Committee

Interim analyses for safety and efficacy will be conducted, using unblinded data, under the guidance of an independent DMC. The DMC will consist of at least 3 members, including a chair, a physician, and a statistician. The DMC will communicate any recommendations based on interim analysis to the sponsor. If necessary, the sponsor may form an Independent Review Committee to review and act upon the recommendations of the DMC. Details will be specified in a separate DMC charter.

10.1.5.2. Early Safety Data Review

Case unblinding may be performed for above reviews if necessary.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or pharmacogenetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an Independent Review Committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, clinical study report, blank or annotated CRFs, will be provided in a secure data sharing environment for up to 2 year per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system(s) will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global PC management system.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in 10.1.7.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of abemaciclib or after abemaciclib become(s) commercially available for treatment of mHSPC.

Sample Type	Custodian	Retention Period After Last Participant Visit[a]
Pharmacokinetics	Sponsor or Designee	Up to 1 year
Genetics	Sponsor or Designee	Up to 7 years
Biomarkers	Sponsor or Designee	Up to 7 years

[a] Retention periods may differ locally.

The sponsor has a right to retain a portion of submitted biopsy tissue. Archival blocks will be returned to the study site. Slides and tissue samples collected on study will not be returned.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory or by the local laboratory as indicated.
- Enrollment and treatment decisions may be based on local laboratory results. A duplicate sample must still be sent to the central laboratory. Differences between these samples will not constitute a protocol deviation. The local laboratory must be qualified in accordance with applicable local regulations.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Sponsor-designated laboratory.
Hematocrit	
Hemoglobin	
Erythrocyte count (RBCs)	
Mean cell volume	
Mean cell hemoglobin concentration	
Leukocytes (WBC)	
Differential (Percent or Absolute Counts) - Neutrophils, segmented - Neutrophils, bands (if detected, and reported separately from segmented neutrophils) - Lymphocytes - Monocytes - Eosinophils - Basophils Absolute Neutrophil Count (segmented and bands) (calculation)	
Platelets	
Clinical Chemistry (non-fasting)	Assayed by Sponsor-designated laboratory.
Alanine aminotransferase (ALT)	
Albumin	
Alkaline phosphatase (ALP)	
Aspartate aminotransferase (AST)	
Blood urea nitrogen (BUN) or blood urea	
Calcium	
Cholesterol	
Creatine kinase (CK)	
Creatinine	
Cystatin C	

Clinical Laboratory Tests	Comments
Direct bilirubin	
Glucose	
High-density lipoprotein (HDL)	
Lactate dehydrogenase (LDH)	
Low-density lipoprotein (LDL)	
Magnesium	
Phosphorus	
Potassium	
Sodium	
Total bilirubin	
Total protein	
Triglycerides	
Uric acid	
Additional Testing	Assayed by Sponsor-designated laboratory.
Testosterone	
Prostate-specific antigen (PSA)	
Coagulation	Assayed by local laboratory.
Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)	
International normalized ration (INR) or Prothrombin time (PT)	
Urinalysis	Assayed by local laboratory.
Blood	
Glucose	
Ketones	
Nitrate or Urine leukocyte esterase	
Protein	
pH	
Specific gravity	
Additional Hepatic Monitoring	See Section 10.5, Appendix 5.
Pharmacokinetic Samples LY2835219 concentration	Assayed by Sponsor-designated laboratory. Results will not be provided to the investigative sites.
Pharmacogenomics Sample	This genetic sample will originate from the whole-blood sample collected in Section 8.7 for biomarker research.
Biomarker Storage Samples	Assayed by Sponsor-designated laboratory.
Archival tumor tissue	
Optional tumor biopsy	
Plasma (Streck)	
Whole blood	

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, vital signs), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital (involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Planned hospitalization or for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical

events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will use CTCAE version 5.0 (NCI 2017) to assign AE severity grades.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or to the Lilly CRP/CRS by telephone. • Contacts for SAE reporting can be found in the SAE form.

SAE Reporting via Paper Form
• Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the Lilly CRP/CRS. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SAE form.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential	Females are considered a woman of childbearing potential if they have had at least one cycle of menses. Any amount of spotting should be considered menarche.
Women not of childbearing potential	Females are considered women not of childbearing potential if • they have a congenital anomaly such as Mullerian agenesis, • they are infertile due to surgical sterilization, or • they are post-menopausal. Examples of surgical sterilization include: hysterectomy, bilateral oophorectomy, bilateral salpingectomy.

10.4.2. Contraception Guidance

The table below describes contraception guidance for male participants.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for at least 3 months following the last dose of study treatment.
Contraception for men with partners of childbearing potential or pregnant	either remain abstinent (if this is their preferred and usual lifestyle), or • **must use condoms** with effective contraception method during intercourse for the duration of the study, and for at least 3 weeks following the last dose of study treatment.

Examples of highly effective, effective and unacceptable methods of contraception can be found below.

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

See Sections 8.2.2 and 8.2.2.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs – red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs – white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [b]	Anti-actin antibody [c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

a Not required if anti-actin antibody is tested.

b Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

c Not required if anti-smooth muscle antibody is tested.

d Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.6. Appendix 6: Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the informed consent form (ICF)	End of the 30-day short-term follow-up visit	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[a] and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[b] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Within 24 hours of awareness	SAE paper form	N/A
Pregnancy					
Pregnancy in female partners of male participants	After the start of study intervention	1 week after last dose (see Section 8.3.5 for pregnancy outcome follow-up guidance)	Within 24 hours (see Section 8.3.5)	Pregnancy paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

a Death caused by disease progression should not be reported as an SAE.

b Serious adverse events, including death caused by disease progression, should not be reported unless the investigator deems them to be possibly related to study intervention or study participation.

10.7. Appendix 7: Inducers and Strong Inhibitors of CYP3A4

The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated. Please refer to Section 6.8 Concomitant Therapy.

This list is not intended to be exhaustive. With available information continually evolving, the status of every relevant drug cannot be guaranteed. Please consult with the medical monitor in case of any doubt about a potential drug-drug interaction.

Strong Inducers of CYP3A4
Aminoglutethimide
Apalutamide
Carbamazepine (daily dose exceeding 600 mg)
Enzalutamide
Fosphenytoin (see also phenytoin)
Ivosidenib
Lumacaftor
Mitotane
Phenobarbital
Phenytoin
Rifabutin
Rifampicin (rifampin)
Rifapentine
St John's wort

Moderate Inducers of CYP3A4
Bosentan
Carbamazepine (daily dose 600 mg or lower)
Cenobamate
Dabrafenib
Danshen (*Salvia miltiorrhiza*)
Efavirenz
Elagolix
Encorafenib
Etravirine
Genistein
Lopinavir (alone)
Lorlatinib
Modafinil
Nafcillin (intravenous)
Pentobarbital
Primidone
Sotorasib
Thioridazine
Tocilizumab (atlizumab)

Strong Inhibitors of CYP3A4
Atazanavir and cobicistat
Boceprevir

Ceritinib
Clarithromycin
Cobicistat (see atazanavir and cobicistat)
Conivaptan
Danoprevir and ritonavir
Elvitegravir and ritonavir
Fosamprenavir and ritonavir
Grapefruit juice
Idelalisib
Indinavir and ritonavir
Itraconazole
Josamycin
Ketoconazole
Lonafarnib
Lopinavir and ritonavir
Mifepristone
Nefazodone
Nelfinavir
Nirmatrelvir and ritonavir
Posaconazole
Ribociclib
Ritonavir
Saquinavir and ritonavir
Telithromycin
Tipranavir and ritonavir
Tucatinib
Viekirax (paritaprevir and ritonavir and ombitasvir and/or dasabuvir and ribavirin)
Voriconazole

10.8. Appendix 8: Country-specific Requirements

10.8.1. Removal of the Legally Authorized Representative, Legal Guardian, and Parents in Germany

This section describes protocol changes applicable for adult participants in study sites in Germany.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
7.2. Participant Discontinuation/Withdrawal from the Study 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.1.3. Informed Consent Process 10.12. Appendix 12: Abbreviations and Definitions	Deleted references to "legally authorized representative," "legal guardian," "parents"	The German Drug Law (Arzneimittelgesetz – AMG) requires per Paragraph 40 (1-3) and Paragraph 41 (3) that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.

The revised text in the following sections show the changes applicable for adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant will be discontinued from the study in the following circumstances:

- at any time at the participant's own request.
- ~~at the request of the participant's designee (for example, parents or legal guardian).~~
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Section 10.3, Appendix 3:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate~~, or the participant's legally authorized representative~~).

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant ~~or the participant's legally authorized representative,~~ and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants ~~or their legally authorized representatives~~ will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant ~~or the participant's legally authorized representative~~ and is kept on file.

10.12. Appendix 12: Abbreviations and Definitions

Enter	Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~

10.8.1.1. Removal of MUGA scans in Germany

The revised text in the following sections show the changes applicable for adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~.

1.3. Schedule of Activities (SoA)

	Screening		On Treatment[a] Cycle = 28 days			Post-Treatment		Instructions
Cycles/Days	Days prior to Randomization		Every Cycle Day 1	Cycle 1 & Cycle 2 Day 15	Cycle 3 Day 15	Short-Term Follow-up[b] V801	Long-Term Follow-up V802 – 8XX (Q90 Days)	
Interval tolerance	≤28	≤14	±3	±3	±3	±7	±14	Cycle 1 Day 1 should occur ≤7 days after randomization.
Other Clinical Assessments								
Cardiac ECHO ~~or MUGA scan~~	X							Repeat if clinically indicated.

10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances

Other alternative locations:

In exceptional circumstances, imaging procedures required during screening, on-study treatment, or follow-up may be performed at an alternate location than the study site or designated facility. Imaging includes: CT or MRI scan (of chest, abdomen, and pelvis), radionuclide bone scan, MRI/CT (MRI preferred) of the brain (if clinically indicated), and ECHO~~/MUGA scans~~.

10.8.2. Discontinuation of Study Drug in Inadvertently Enrolled Participants in Canada

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow-up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events, Serious Adverse Events, and Product Complaints), and Section 8.2 (Safety Assessments) of the protocol.

10.9. Appendix 9: Protocol JPEG RECIST Criteria 1.1 for Soft Tissue

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria will be used to assess response and progression of soft tissue disease in this study (Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical examination (nonmeasurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are nonmeasurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical examination.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin

lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and CR in rare cases, if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease.

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Response Criteria

Evaluation of Target Lesions

Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response: At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions, cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10 mm short axis).

Non-CR/non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study intervention until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at

that time point. The table immediately below provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Time Point Response: Patients with Target (±Nontarget) Disease

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

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

The table below is to be used when patients have nonmeasurable disease only.

Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease.

[a] non-CR/non-PD is preferred over stable disease for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study intervention. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies in which the beneficial effect therapy is not known, follow-up every 6 to 8 weeks is reasonable. Normally, all target and nontarget sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation

The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in

nonrandomized trials in which response (CR/PR) is the primary endpoint. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trials* (Phase 2 or 3) or studies in which SD or progression is the primary endpoint, confirmation of response is not required. However, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies that are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of study intervention at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR+PR) is the primary endpoint, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

10.10. Appendix 10: Protocol JPEG CTCAE 5.0 Diarrhea/Pneumonitis/ALT and AST Increased Definitions

Diarrhea/Pneumonitis/ALT and AST increased will be evaluated in this study using the criteria proposed by CTCAE v5.0 revised: Gastrointestinal disorders, Respiratory, Thoracic, and Mediastinal Disorders, and Investigations.

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastrointestinal Disorders					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by an increase in frequency and/or loose watery bowel movements.					
Respiratory, Thoracic, and Mediastinal Disorders					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (for example, tracheotomy or intubation)	Death
Definition: a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					

Investigations					
Alanine aminotransferase (ALT) increased	>ULN through 3.0 x ULN if baseline was normal; 1.5 through 3.0 x baseline if baseline was abnormal	>3.0 through 5.0 x ULN if baseline was normal; >3.0 through 5.0 x baseline if baseline was abnormal	>5.0 through 20.0 x ULN if baseline was normal; >5.0 through 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Death
Definition: a finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Aspartate aminotransferase (AST) increased	>ULN through 3.0 x ULN if baseline was normal; 1.5 through 3.0 x baseline if baseline was abnormal	>3.0 through 5.0 x ULN if baseline was normal; >3.0 through 5.0 x baseline if baseline was abnormal	>5.0 through 20.0 x ULN if baseline was normal; >5.0 through 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Death
Definition: a finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					

Abbreviations: ADL = activities of daily living; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal.

10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this Appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in consultation with the investigator.

Exceptional Circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing Changes under Exceptional Circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

Additional notification to these groups will not typically be required unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for Making a Change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making such changes are compliance with GCP, enabling participants to continue safely in the study, and maintaining the integrity of the study.

Informed Consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined below in Section 1, Remote visits
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional Circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct (for example, telemedicine versus on-site) will not be considered protocol deviations.

1. Remote visits

In exceptional circumstances, study visits may be done remotely using telemedicine. In source documents and the CRF, the study site must capture the visit method, with a specific explanation for any data missing and document as protocol violations, when applicable.

Telemedicine:

Telemedicine visits using interactive technology-assistance (that is, at a minimum video and/or audio technology) may be performed by an investigator in lieu of on-site visits to complete required study assessments as outlined in Section 1.3.

Study procedures that may be performed by an investigator using telemedicine include the following:

- Informed consent
- Inclusion/exclusion assessments; medical history
- Telehealth physical examination (if allowed by local regulation)
- AE assessments; review and update on concomitant medications
- ECOG performance status
- Evaluation of symptomatic progression
- PRO assessments; review of patient diary; drug compliance evaluations for all study intervention
- Survival status; post-discontinuation anticancer therapies.

Other alternative locations:

In exceptional circumstances, imaging procedures required during screening, on-study treatment, or follow-up may be performed at an alternate location than the study site or designated facility. Imaging includes: CT or MRI scan (of chest, abdomen, and pelvis), radionuclide bone scan, MRI/CT (MRI preferred) of the brain (if clinically indicated), and ECHO/MUGA scans. See Section 1.3 for details.

The protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participant and the site staff.

2. Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

3. Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study intervention or study tools (for example, participant diaries) during regularly scheduled on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant's caregiver or designee to go to the site and receive study intervention or study tools on a participant's behalf, or
- arranging delivery of study intervention and/or study supplies.

These requirements must be met and documented in the participant's medical records before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise intervention blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study intervention.
- When delivering study intervention to a location other than the study site (for example, participant's home), the investigator or designated site staff should follow local regulation and ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions should be provided to the participant or caregiver on the final disposition of any unused study intervention, empty product bottles, or completed patient diaries.

4. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments completed during screening are required as outlined in the protocol.

In exceptional circumstances, Cycle 1 Day 1 visit must occur within 35 days from date of signed informed consent and will not constitute as a protocol violation. Any screening procedures that fall outside of the required windows per the SoA (Section 1.3) must be repeated. See Section 5.4 for additional details on screen failures.

Participants who are unable to complete screening within the 35-day window and are not able to repeat screening procedures will be documented in CRF as a screen failure due to exceptional circumstances.

5. Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA outlined in Section 1.3. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Day 1 of all cycles	The relative day within dosing cycle and visit window may be adjusted to ±5 days.
All other treatment visits	Follow SoA (Section 1.3).

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented:

- Sites will document all remote visits in the study files and CRF (where applicable) including telemedicine, local imaging and procedures, study intervention, or screening period guidance. Documentation should include details of which participants, visits type, and study procedures were affected by exceptional circumstances.
- Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents generated during a telemedicine visit should be part of the investigator's source documentation.

10.12. Appendix 12: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence.
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AQA	Analgesic Quantification Algorithm
AR	androgen receptor
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-versus-time curve
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an auxiliary medicinal product.
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product.
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial.
BICR	blinded independent-central review
CCI	[redacted]

blinding	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BP	blood pressure
BPI-SF	Brief Pain Inventory-Short Form
CDK	cyclin dependent kinase
CDK4 & 6	cyclin dependent kinase 4 and 6
CFR	code of federal regulations
CI	confidence interval
CK	creatine kinase
CNS	central nervous system
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CR	complete response
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRP/CRS	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP/CRS may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRPC	castration-resistant prostate cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYCLONE 1	Study I3Y-MC-JPCY

CYCLONE 2	Study I3Y-MC-JPCM
CYCLONE 3	Study I3Y-MC-JPEG
D1	a protein that helps control cell division.
DBL	direct bilirubin
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DRFS	distant relapse free survival
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
Enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	European Quality of Life – 5 dimensions – 5 level
ER	estrogen receptor
ER+	estrogen receptor positive
ET	endocrine therapy
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FACT-G	Functional Assessment of Cancer Therapy – General
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal

HER2-	human epidermal growth factor receptor 2 negative
HR	hazard ratio
HR+	hormone receptor positive
HS	hormone sensitive
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDFS	invasive disease-free survival
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	interstitial lung disease
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	Institutional Review Board
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system

LHRH	luteinizing hormone-releasing hormone
MATE1	multidrug and toxin extrusion protein 1
MBC	metastatic breast cancer
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
mHSPC	metastatic hormone-sensitive prostate cancer
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription.
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition scan
NE	not evaluable
NIMP	Non-investigational Medicinal Product. See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
NR	not reached
NRS	numeric rating scale
ORR	objective response rate
OS	overall survival

participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PC	product complaint
PCWG	The Prostate Cancer Clinical Trials Working Group
PCWG2	The Prostate Cancer Clinical Trials Working Group 2
PCWG3	The Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PPS	per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PR	partial response
PRO	patient-reported outcomes
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PT-INR	prothrombin time – international normalized ratio
QD	once daily
QTc	corrected QT interval
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
rPFS	radiographic progression-free survival
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

SoA	schedule of activities
SOC	system organ class
SSE	symptomatic skeletal event
SMD	senior management designee
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
VTE	venous thromboembolic event

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [d] (18-Jul-2023)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment d

The protocol was amended to adjust the timing of the futility analysis to account for actual enrollment rate and to possibly be conducted in conjunction with a planned safety review. In addition, minor changes were made to correct a typographical error introduced in the previous amendment regarding the imaging procedure; and to clarify on: the collection of ethnicity, cycle delays due to logistical reasons, diarrhea management, and clinical laboratory tests. The table listing strong and moderate inducers and strong inhibitors of CYP3A4 was also updated.

Changes and rationale are summarized in the table below; minor typographical or formatting edits are not presented in the table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) and 4.2. Scientific Rationale for Study Design	"ethnicity" was added to the instructions in the demographics line item. "ethnicity" was added in the 2 sentences in final paragraph.	Clarification Together with race, ethnicity will also be collected.
1.3. Schedule of Activities (SoA)	Corrected a typographical error introduced in the previous amendment (c). Reverted to original text to now read "CT or MRI of chest, abdomen, and pelvis AND Whole-body bone scan"	Editorial
6.2.1. Selection and Timing of Doses	In the first sentence in the fourth paragraph, added "or vacation"	Clarification
6.8.2. Supportive Management for Diarrhea	In the second to last paragraph, deleted "broad-spectrum antibiotics such as fluoroquinolones must be prescribed" and added "antibiotics should be considered"	Clarification
8.1. Efficacy Assessments	Corrected a typographical error introduced in the previous amendment (c). In the second paragraph, reverted to original text to now read "For all patients,	Editorial

Section # and Name	Description of Change	Brief Rationale
	imaging (CT or MRI of the chest, abdomen, and pelvis and radionuclide bone scan) will be performed…"	
9.3. Analyses Sets	Deleted "and have baseline" from description of PK analysis population	Clarification
9.4.2. Primary Endpoint/Estimand Analysis	Updated timing of futility analysis in third paragraph and in the Statistical Analysis Milestones table. Added sentence at the end of the third paragraph	To ensure adequate follow-up time at the time of the futility analysis, after accounting for actual rate of enrollment to the study. Additionally, for logistical reasons, enabling an interim analysis to be conducted at the time of a planned safety review per the IDMC's recommendation
10.2. Appendix 2: Clinical Laboratory Tests	In the "Differential" line item, replaced "and "with "or", to read "(Percent or Absolute Counts)"	Clarification
10.7. Appendix 7: Inducers and Strong Inhibitors of CYP3A4	Updated table listing strong and moderate inducers and strong inhibitors of CYP3A4	Update

Amendment [c] (20-Oct-2022)

This amendment is considered to be substantial because it is likely to have a significant impact on eligibility for study participation.

Overall Rationale for the Amendment c

The primary reason for this amendment is to address external investigator feedback, as summarized below

- exclude participants who received prior docetaxel for metastatic prostate cancer in accordance with the evolving mHSPC treatment landscape and to limit heterogeneity of the study population.
- allow the high-risk criteria to be confirmed independent of the ADT initiation, to conform to current and anticipated changes in diagnostic and clinical practice, and
- allow one course of palliative radiotherapy or surgery during study without requiring participants to discontinue study intervention to align with clinical practice and recommendations for symptom management.

Changes and rationale are summarized in the table below; minor typographical or formatting edits are not presented.

Section # and Name	Description of Change	Brief Rationale
Title page and 1.1. Synopsis	Updated the EU trial number from 2022-500461-28-00 to 2022-500461-28-06	To reflect the current number on CTIS
1.1. Synopsis	Study Population, second paragraph: updated the description of the systemic treatment permitted prior to randomization	For consistency with the revised inclusion criterion [4] and exclusion criterion [12]
	Study Population, fourth paragraph: deleted "pituitary disorder"	For consistency with the revised exclusion criterion [21]
1.1. Synopsis, 1.2. Schema, and 4.1. Overall Design	Stratification factors: deleted "prior docetaxel"	For consistency with revisions to exclusion criterion [12]
1.1. Synopsis, 3. Objectives, Endpoints, and Estimands	Deleted "and/or symptomatic" • Section 1.1: Treatment Arms and Duration, Blinded study drug, last paragraph, second sentence • Section 3: Primary estimand, second paragraph, third major bullet (Treatment condition), second sentence	For consistency with change made in Sections 6.8 and 7.1.
1.3. Schedule of Activities (SoA)	The imaging row (CT of chest or CT/MRI of abdomen and pelvis AND whole-body bone scan): Updated the row stub	For consistency with revisions in Section 8.1
	Updated the comments for the "On Treatment" and "Instructions" columns.	Clarity and consistency with revised Sections 6.8 and 7.1, as well as Section 8.1
5.1. Inclusion Criteria	Updated the following inclusion criteria:	
	• 2: added "predominant"	Clarity
	• 3: updated to allow the high-risk criteria to be confirmed independent of the ADT initiation.	To conform to current and anticipated changes in diagnostic and clinical practice
	• 4: clarified the prior ADT requirement	Clarity
	• 6:	Correction

Section # and Name	Description of Change	Brief Rationale
	○ updated the unit of measure for serum potassium: from "mM" to "mmol/L"	
	○ updated criteria for baseline renal function to be based on eGFR instead of serum creatinine	For consistency with clinical practice
	• 8: updated the contraception requirements	For consistency with changes to Section 10.4, Appendix 4
5.2. Exclusion Criteria	Updated the following exclusion criteria:	
	• 12: ○ deleted prior docetaxel ○ referred to inclusion criterion [4] for prior ADT	Participants who received prior docetaxel for metastatic prostate cancer will no longer be eligible per external recommendations, in accordance with the evolving mHSPC treatment landscape and to limit heterogeneity of the study population.
	• 13: ○ updated the description of the radiation therapy ○ updated the window for permitted palliative radiation or surgical therapy from 4 weeks to 2 weeks prior to randomization	Clarity
	• 21: deleted "or pituitary disorder"	Clarity
	• 22: updated the window for a major surgery from 4 weeks to 2 weeks prior to randomization	Consistency with the revised exclusion criterion [13].
	• 23: added "or" ("who are in remission and/<u>or</u> whose likelihood of recurrence …")	Clarity
5.3. Lifestyle Considerations	Updated the contraception requirements	For consistency with changes to Section 10.4, Appendix 4.

Section # and Name	Description of Change	Brief Rationale
6.1.2. Background Therapy or Standard-of-Care	Revised the following sentence to read "The choice of LHRH agonist/antagonist will be physician's choice~~ and supplied by the site~~."	Flexibility
6.3.3. Emergency Unblinding	Third sentence: deleted "make every effort to"	Clarity
6.5.2. Dose Modifications - Abemaciclib/Placebo	Second paragraph: updated to read "Participants undergoing ~~non-tumor related~~ surgical procedures …"	Clarity
	Toxicity Dose Modifications table: updated the VTE-related information and presented it all in a separate row at the end of the table.	For consistency with dose modifications used when VTE occurs during abemaciclib treatment for approved indications (such as MBC)
6.8. Concomitant Therapy	Modified to allow one course of palliative radiotherapy or surgery during study	To align with clinical practice and recommendations for symptom management
7.1. Discontinuation of Study Intervention	Removed the requirement to discontinue study intervention for participants with symptomatic progression	For consistency with change made in Section 6.8
	Updated the description of scheduled assessments following discontinuation	Clarity
8.1. Efficacy Assessments	Updated information pertaining to imaging	For consistency with the revised exclusion criteria [12] and [13]
8.2.5. Guidance for Venous Thromboembolic Events	Last paragraph: replaced "hon-hematologic toxicities" with "VTE"	Per revisions in Section 6.5.2
9.4.3.3. Castration-Resistant Prostate Cancer (CRPC)-free Survival	Added a reference to Section 9.4.3.5	Clarity

Section # and Name	Description of Change	Brief Rationale
10.4. Appendix 4, Contraceptive and Barrier Guidance	10.4.1. Definitions Updated the definition of women not of childbearing potential	Per updated internal contraception guidance and to be aligned with the abiraterone label
	10.4.2. Contraception Guidance Updated	
Old page 141, with manually added approvers' names	Deleted.	This information will be generated automatically in the Lilly document management system.

Amendment [b] (05-Aug-2022)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment b:

The Study JPEG protocol was amended to address the Request for Information by the European Medicines Agency. Changes are summarized in the table below; minor typographical or formatting edits are not presented.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added clarifying language regarding on study brain imaging for patients with history of pretreated CNS metastases	Clarification
5.1. Inclusion Criteria	Amended inclusion criterion 4 to allow for patients starting ADT to continue first generation anti-androgen for 2 weeks after Cycle 1 Day 1	Per regulatory feedback
5.2 Exclusion Criteria	Removed testosterone lab values (≤50 ng/dL; ≤1.73 nmol/L) from exclusion criteria 11	Clarification
6.8. Concomitant Therapy	Added language regarding the avoidance of live vaccines during, and up to 90 days after the last dose of study treatment	Per regulatory request
7.2.1. Discontinuation of Inadvertently Randomized Patients	Updated title to: "Discontinuation of Inadvertently ~~Enrolled~~ Randomized	Administrative

Section # and Name	Description of Change	Brief Rationale
	Patients"; deleted language regarding inadvertently enrolled patients	
10.1.4 Data Protection	Added reference to the General Data Protection Regulation and the European Clinical Trial Regulation Articles 56, 57, 58	Per regulatory request
10.8.1.1. Removal of MUGA scans in Germany	Added new subsection for study sites in Germany; Removed MUGA scans for study sites in Germany	Per regulatory request
Throughout	Updated "analogues" to "agonist/antagonist"	Clarification

Amendment [a]: (25-Mar-2022)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The Study JPEG protocol was amended to clarify the investigator's responsibility per Regulation No. 536/2014 and to simplify the table related to study interventions in Section 6.1. Changes are summarized in the table below; minor typographical or formatting edits are not presented.

Section # and Name	Description of Change	Brief Rationale
6.1. Study Intervention(s) Administered	In the table - Deleted the rows for investigational status, type, formulation, and strength(s) of study interventions - Deleted the LHRH analogue column - Replaced yes or no by text to clarify EU authorization status - Deleted footnote a	Deletion/Editorial
10.1.1. Regulatory and Ethical Considerations	- Added "Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity."	Clarification

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