Protocol I3Y-MC-JPCY(b)

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

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Title Page

Protocol Title: 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

Protocol Number: I3Y-MC-JPCY

Amendment: (b)

Compound: LY2835219

Study Phase: Phase 2

Short Title: Abemaciclib in Men with Heavily Treated Metastatic Castration-Resistant Prostate Cancer

Acronym: JPCY

Sponsor Name: Eli Lilly and Company

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Protocol I3Y-MC-JPCY(a) Electronically Signed and Approved by Lilly on 24-Sep-2020
Protocol I3Y-MC-JPCY(b) 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 (a)	24-Sep-2020
Protocol I3Y-MC-JPCY	18-Mar-2020

Amendment (b)

This amendment is considered to be substantial 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:

Protocol amendment(b) for Study JPCY protocol was amended to update the dose modification guidance and safety monitoring. These updates are in alignment with changes made in the development core safety information of the Investigator's Brochure (IB).

In addition, minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol.

Section # and Name	**Description of Change**	**Brief Rationale**
1.3. Schedule of Activities	Added clarification to vital signs that procedure does not repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to initiating abemaciclib	Addition
1.3.1. Sampling Schedule for Pharmacokinetics and Biomarkers	Deleted text from footnote b to align with Inclusion Criterion 9	Deletion
5.3. Lifestyle Considerations	Added 'affect prostate specific antigen levels' for participants who must not take preparations or herbal products and removed 'endocrine effects'	Addition
6.2.1. Selection and Timing of Doses	Added language to discuss with Lilly CRP/CRS prior to dispensing additional study treatment	Addition
6.5. Concomitant Therapy	Updated language for CYP3A modulators and transporter substrates	Update to align with current guidance
6.6.2. Toxicity Dose Adjustments and Delays of Abemaciclib	Formatted table for dose adjustments and delays of abemaciclib	Formatting; to align with IB update
6.6.2. Dose Adjustments and Delays Abemaciclib	Added AST to the dose modification table for increased transaminases	To align with IB update
	Removed VTE specific guidance for dose modifications to follow non-hematologic dose adjustment guidance	To align with IB update

8.2.2.2. Guidance for Monitoring Renal Function	Updated renal function monitoring language	To align with IB update
8.2.2.3. Guidance for Venous Thromboembolic Events	Updated VTE safety monitoring language	To align with IB update
8.2.2.4. Guidance for Interstitial Lung Disease/Pneumonitis	Updated ILD/pneumonitis safety monitoring language	To align with IB update
9.2. Sample Size Determination and 9.4.2 Primary Analysis	Editorial changes to clarify study statistics	Editorial
10.7. Appendix 7	Added ALT and AST to the CTCAE 5.0 table and updated Appendix title and summary text to reflect these additions	Addition

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1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Short Title: Abemaciclib in Men with Heavily Treated Metastatic Castration-Resistant Prostate Cancer

Rationale:

Prostate cancer is the second most common cancer in men and the fifth leading cause of cancer deaths among men worldwide. Despite the initial sensitivity of advanced prostate cancer to androgen-deprivation therapy, most patients eventually develop castration-resistance. Persistent or reactivated androgen receptor (AR) signaling and/or activation of pathways involved in crosstalk with AR signaling are key drivers of progression to metastatic castration-resistant prostate cancer (mCRPC), an incurable and lethal stage of the disease.

The cyclin/cyclin-dependent kinase (CDK)/retinoblastoma protein (pRb)-axis is a critical modulator of cell cycle entry and is commonly altered in cancers. Evidence suggests that AR signaling promotes enhanced translation of the D-type cyclins resulting in CDK4 and CDK6 (CDK4&6) activation, pRb hyperphosphorylation and cell cycle progression.

Abemaciclib is an oral and potent ATP-competitive inhibitor of CDK4&6 that is administered on a continuous dosing schedule. Abemaciclib is approved by major global regulatory authorities for the treatment of patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC) in combination with an aromatase inhibitor as initial endocrine-based therapy and with fulvestrant following endocrine therapy. In addition, abemaciclib is also approved as monotherapy for heavily pre-treated (following endocrine therapy and chemotherapy) HR+, HER2- MBC patients by the Food and Drug Administration.

Preclinical studies in cell cultures and mouse xenograft prostate cancer models showed that single agent abemaciclib induces cell cycle arrest and tumor growth inhibition (data on file). The clinical activity of abemaciclib in combination with abiraterone and prednisone is currently investigated in a randomized placebo-controlled Phase 2 study in patients with mCRPC (I3Y-MC-JPCM [CYCLONE 2], NCT03706365).

Treatment of advanced prostate cancer is palliative and therapeutic options are limited for mCRPC patients whose disease had progressed after life-prolonging therapies. Hence, there is an important unmet need for these patients that warrants the development of therapies with novel mechanisms of action.

This open-label single-arm Phase 2 study will assess the safety and efficacy of abemaciclib monotherapy in heavily pretreated mCRPC patients who received at least 1 novel hormonal agent and 2 taxane regimens.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the efficacy of abemaciclib monotherapy.	• Investigator-assessed ORR per RECIST 1.1.
Secondary	
• To further characterize the clinical activity of abemaciclib monotherapy.	• rPFS • OS • DoR • DCR • PSA response rate • Time to PSA progression • Time to symptomatic progression
• To characterize the safety profile of abemaciclib.	• Assessment of safety including, but not limited to, the following: AEs, SAEs, physical examination, and clinical laboratory abnormalities per CTCAE v5.0
• To explore patient reported tolerability of abemaciclib monotherapy (including symptomatic AEs and overall side-effect burden), patient reported pain intensity, physical functioning, and overall health related quality	• PRO-CTCAE • FACT-GP5 • 7-day Worst Pain Numeric Rating Scale • EORTC QLQ-C30 Physical Functioning Scale • EORTC QLQ-C30 Global Health Status/QoL Scale
• To characterize the PK of abemaciclib and its metabolites.	• Concentrations of abemaciclib and its metabolites.
• To characterize Ki-67 baseline expression	• % of cells expressing Ki-67 by IHC

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events v5.0 (NCI 2017); DCR = disease control rate; DoR = duration of response; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-GP5 = Functional Assessment of Cancer Therapy- General; IHC = immunohistochemistry; Ki-67 = protein encoded by the MKI67 gene; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; PSA = prostate specific antigen; PRO-CTCAE = Patient Reported Outcome-Common Terminology Criteria for Adverse Events v5.0 (NCI 2017); QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1 (Eisenhauer et al; 2009); rPFS = radiographic progression-free survival; SAE = serious adverse event.

Overall Design

CYCLONE 1 is an open-label, single-arm, global multi-center, Phase 2 study to assess the safety and efficacy of abemaciclib monotherapy in patients with mCRPC.

The study population consists of patients with progressive mCRPC (by prostate-specific antigen [PSA] and/or imaging) who have previously received, in the metastatic hormone-sensitive setting and/or in the castration-resistant settings, at least 1 novel hormonal agent (abiraterone acetate, apalutamide, darolutamide or enzalutamide), and 2 taxane regimens (docetaxel and cabazitaxel).

Number of Participants:

Approximately 40 participants with mCRPC will be treated in this study.

Intervention Groups and Duration:

Eligible participants will receive abemaciclib 200 mg orally twice daily on a continuous 28-day dosing schedule. Abemaciclib can be taken with or without food, at approximately the same times each day, with at least 6 hours between doses.

Data Monitoring Committee: No

1.2. Schema

CYCLONE 1 – A Phase 2, open-label, single-arm, global multi-center study

Participants
(key inclusion criteria)

- Adult men with mCRPC
- Progressive disease (by PSA and/or imaging)
- Serum testosterone ≤1.73 nmol/L (≤50 ng/dL)
- Previously received (in the metastatic hormone-sensitive setting and/or in the castration-resistant settings) :
  - ✓ ≥ 1 novel hormonal agent (abiraterone acetate, apalutamide, darolutamide or enzalutamide)
  - ✓ 2 taxane-based chemotherapy regimens (docetaxel, cabazitaxel)
- Up to 3 prior systemic therapy regimens for mCRPC
- Measurable disease per RECIST1.1
- Willing and amenable to undergo tumor biopsy of a metastatic lesion

Study Intervention (n=40)

- Abemaciclib administered orally at 200 mg twice daily on a continuous dosing schedule (28-day cycle)

Until disease progression (symptomatic and/or radiographic), the occurrence of unacceptable treatment-related toxicity or until a discontinuation criterion is met.

Primary endpoint

- Investigator-assessed Objective Response Rate per RECIST 1.1

Key Secondary endpoints

- Safety, rPFS, OS, PSA response rate, Time to PSA progression, Time to symptomatic progression, PRO, and PK.

Abbreviations: mCRPC = metastatic castration resistant prostate cancer; n = number of participants; OS = overall survival; PK = pharmacokinetics; PRO = patient reported outcome; PSA = prostate specific antigen; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.; rPFS = radiographic progression-free survival.

1.3. Schedule of Activities (SoA)

This section includes the following SoAs:

- Screening, On-Treatment and Post-Treatment SoA
- Continued Access SoA
- Sampling Schedule for Pharmacokinetics and Biomarkers

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**V801** (30 days ±7)	**V802-8XX** (90 days ±14)	
Documentation and Examination										
Informed Consent	X									Written informed consent must be obtained within 28 days prior to Cycle 1 Day 1 AND prior to conducting any protocol-specific tests/procedures.
Inclusion/ Exclusion Criteria	X									See Sections 5.1 and 5.2
Medical History	X									Including assessment of preexisting conditions, historical illnesses, prior anticancer therapies (including systemic, local, and surgical), and habits (such as tobacco and alcohol use).
Prior and Concomitant Medication	X		X					X		At screening, record prior and concurrent medications. Record all premedications, supportive care, and concomitant medications including over-the-counter and analgesics use, continuously at every visit and throughout the study.
Physical Examination		X	X	X	X	X	X	X		Perform prior to administering abemaciclib. Includes height (only at screening) and weight. Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation. Additional exams should be

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
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										performed as clinically indicated.
Vital Signs		X	X	X	X	X	X	X		Perform prior to administering abemaciclib. Collect temperature, blood pressure, pulse oximetry, and pulse rate. Repeat if clinically indicated. Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation.
ECOG Performance Status		X	X		X		X	X		Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation.
Other Clinical Assessments										
12-Lead ECG	X							X		Single ECG performed locally. 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.
AE Assessment	X		X					X	X	Collect continuously at every visit and throughout the study using CTCAE Version 5.0. See Section 8.3 for further details on AE and SAE reporting.

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
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Laboratory Assessments										
Hematology		X	X	X	X	X	X	X		See Section 10.2, Appendix 2. Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation. Repeat if clinically indicated.
Chemistry		X	X	X	X	X	X	X		See Section 10.2, Appendix 2. Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation. Repeat if clinically indicated. Refer to Sections 8.2.2.1 and 10.5, Appendix 5, for hepatic monitoring.
PSA		X	X		X		X	X		See Section 10.2, Appendix 2.
Testosterone		X	X		X		X	X		See Section 10.2, Appendix 2.

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
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Tumor Assessment										
CT or MRI Scan of Chest, Abdomen, and Pelvis	X		Every 8 weeks, independent of treatment delays, (Day 1 of Cycle 3, 5, 7, 9, 11, etc…)					X	X	Perform within 7 days prior to scheduled calendar day (except in screening period). Unscheduled assessments if signs of disease progression are observed. Perform within 14 days of symptomatic progression (if no radiographic progression yet) and prior to the start of new anticancer therapy, palliative radiotherapy or surgery. Patients discontinuing abemaciclib prior to documented radiographic progression will continue to have scheduled disease assessments until documented radiographic progression, start of new anticancer therapy, withdrawal of consent, death, or study completion, whichever occurs first.
Radionuclide Bone Scan	X		Every 8 weeks, independent of treatment delays, (Day 1 of Cycle 3, 5, 7, 9, 11, etc…)					X	X	

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
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MRI (preferred) or CT Scan of Brain	X									Only required at screening for patients with suspicion and/or symptoms of CNS involvement to rule out CNS metastases. Unscheduled assessments if signs of CNS disease progression are observed.
Symptomatic Progression			X		X		X	X	X	Assess: • Symptomatic skeletal event defined as 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 anti-cancer therapy • Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy Perform until evidence of symptomatic disease progression, start of new anticancer therapy, withdrawal of consent, death, or study completion, whichever occurs first.
Study Treatment										

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**V801** (30 days ±7)	**V802-8XX** (90 days ±14)	
Abemaciclib			Orally twice daily, on Days 1 through 28 of a 28-day cycle.							See Section 6.1
Study Drug Compliance Assessment					X		X			Abemaciclib bottle(s), including any unused tablets, will be returned at the beginning of every cycle starting at Cycle 2 Day 1 and at abemaciclib discontinuation for drug accountability
Review Patient Diary				X	X	X	X			Review patient diary at each study visit for completion of date and time for each dose taken on the day before PK sampling. After Cycle 3 Day 1, the diary is no longer required.
Post-study Treatment Collections										
Post-Discontinuation Anti-Cancer Therapies								X	X	Collect until death, withdrawal of consent, or study completion.
Survival Status								X	X	Although preferable to collect during a clinic visit, if no procedures are required, survival information may be collected by contacting the patient or family directly (e.g., via telephone. This should be collected at minimum every 90 (±14) days if no other procedures are performed.

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**V801** (30 days ±7)	**V802-8XX** (90 days ±14)	
Pharmacogenomic, Biomarker and PD Assessment										
Tumor Biopsy	See Section 1.3.1							See Section 1.3.1		See Section 8.8
CCI			CCI					CCI		CCI
PK Sampling										
PK			See Section 1.3.1							See Section 8.5
Patient Reported Outcomes										
7-day Worst Pain NRS	X		X		X		X	X		See Section 8.10 PRO questionnaires should be administered in the following order: 7-day Worst Pain NRS, then PRO-CTCAE, then FACT-GP5, and finally the EORTC QLQ-C30 Physical Functioning and Global Health Status/QoL scales.
PRO-CTCAE	X		X		X		X	X		See Section 8.10

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**Post-Treatment Follow-up**		**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 and subsequent**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	Procedures and disease assessments (tumor imaging) should be performed as per the schedule of activities, according to the calendar days, regardless of treatment delays.
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**V801** (30 days ±7)	**V802-8XX** (90 days ±14)	
FACT-GP5	X		X		X		X	X		See Section 8.10
EORTC QLQ-C30 Physical Functioning Scale	X		X		X		X	X		See Section 8.10
EORTC QLQ-C30 Global Health Status/QoL	X		X		X		X	X		See Section 8.10

Abbreviations: AE = adverse event; CNS = central nervous system; CT = computed tomography; CTC = circulating tumor cells; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-GP5 = Functional Assessment of Cancer Therapy- General; MRI = magnetic resonance imaging; n = number; NRS = numeric rating scale; PD = pharmacodynamics; PGx = pharmacogenomics; PK = pharmacokinetics; PRO = patient-reported outcome; PRO-CTCAE = Patient-reported outcome Common Terminology Criteria for Adverse Events; PSA = prostate specific antigen; QoL = quality of life; SAE = serious adverse event; V = visit.

[a] Short-term follow-up begins when the participant and investigator agree that the participant will no longer continue study treatment and lasts approximately 30 days (±7 days).

[b] Long-term follow-up begins when the short-term follow-up period is completed and continues until the participant's death, loss to follow-up, or study withdrawal.

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

Mobile healthcare service may be leveraged to collect and process lab samples in conjunction with a patient's visit, when deemed appropriate by the investigator and allowed by local laws and regulations.

Continued Access Schedule of Activities			
Study phase	**Continued Access Treatment**	**Follow-up[a]**	**Instructions**
	V501-V5XX	**V901**	
Procedure			
Abemaciclib	X		Orally twice daily on Days 1 through 28 of a 28-day cycle.
AE collection	X	X	Assessments to be conducted at a minimum with each collection and dispensing study drug (every 28 days) from Visits 501-5XX. After V801, only SAEs that are related to study intervention or protocol procedure will be collected. Frequency of evaluation, including efficacy assessments, is left to the judgement of the investigator based on standard of care.

Abbreviation: AE = adverse event; SAE = serious adverse event; V = visit.

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

1.3.1. Sampling Schedule for Pharmacokinetics and Biomarkers

Sampling Day	Tumor Biopsy	CCI	Plasma and blood microsample (PK)[a]
Baseline (Day −28 to Day −1)	X[b] (mandatory)		
Cycle 1 Day 1 (Pre-dose)		CCI	
Cycle 1 Day 1 (Post-dose)			X[d]
Cycle 1 Day 15 (Pre-dose)			X[e]
Cycle 2 Day 1 (Pre-dose)		CCI	X[e]
Cycle 2 Day 15 (Pre-dose)			X[e]
Cycle 3 Day 1 (Pre-dose)			X[e]
Cycle 4 Day 1 (any time during visit)		CCI	
End of treatment or Short-term follow-up (Visit 801), prior to start of new anti-cancer therapy	X[g] (optional)		

Abbreviations: eCRF = electronic case report form; CRP = clinical research physician; CRS = clinical research scientist; CTC = circulating tumor cells; PGx = pharmacogenomics; PK = pharmacokinetics.

a The date/time of the first abemaciclib dose on Cycle 1 Day 1 should be recorded in the eCRF. After Cycle 1 Day 1, the date and times (am/pm) of abemaciclib doses taken on the day prior to PK sampling should be recorded in the patient diary.

b Participants must have a metastatic lesion amenable to biopsy (core needle) for biomarker analysis. Soft-tissue biopsy is preferred to bone biopsy whenever possible. Biopsy of newly emerged radiographic metastases preferred to biopsy of previously existing lesions whenever possible. Adequate archival metastatic tissue can be used in lieu of a new biopsy and if the biopsy was done within 12 weeks prior to enrollment and no treatment was initiated from biopsy to study entry.

c CCI

d For Cycle 1 Day 1, PK sampling should occur any time 30 minutes after first abemaciclib dose. The blood microsample should be taken within (+/-) 10 minutes of the plasma PK sample. The date and times of all PK samples must be accurately recorded.

e For Cycle 1 Day 15 and all subsequent PK samples, PK sampling should occur in the morning before the first abemaciclib dose of the day. The blood microsample should be taken within (+/-) 10 minutes of the plasma PK sample. The date and times of all PK samples must be accurately recorded.

f CCI

g Optional biopsy of metastatic lesion at the time of radiographic progression will be considered only if participant has completed at least 4 cycles of abemaciclib. The biopsy of a newly emerged or a progressing metastasis is preferred.

h CCI [redacted]

Mobile healthcare service may be leveraged to collect and process PK and CCI [redacted] in conjunction with a patient's visit, when deemed appropriate by the investigator and allowed by local laws and regulations

2. Introduction

2.1. Study Rationale

Cyclin-dependent kinases 4 and 6 (CDK4&6) inhibitors have recently emerged as a standard of care for the management of hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (MBC). Abemaciclib is an oral, selective, and potent adenosine triphosphate (ATP)-competitive inhibitor of CDK4&6 that is dosed on a continuous schedule. Abemaciclib is approved by major global regulatory authorities for the treatment of patients with HR+, HER2- MBC in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy and with fulvestrant following endocrine therapy. In addition, abemaciclib is also approved as monotherapy for heavily pre-treated (following endocrine therapy and chemotherapy) HR+, HER2- MBC patients by the Food and Drug Administration (FDA).

Persistent or reactivated androgen receptor (AR) signaling pathway through molecular adaptations (such as AR amplification, overexpression, mutations, or the expression of constitutively active variants) and/or activation of pathways involved in crosstalk with AR signaling are key drivers of castration-resistant prostate cancer (CRPC). Similar to the estrogen receptor signaling pathway in breast cancer, there is evidence that the AR signaling pathway interacts with the CDK4&6 and retinoblastoma protein (pRb) axis to sustain prostate cancer cell proliferation and survival (Knudsen et al. 1998; Xu et al. 2006). It has been established that androgens induce cell-cycle progression, in part through mammalian target of rapamycin-dependent translation of D-cyclins and subsequent activation of CDK4&6 and pRb hyperphosphorylation (Xu et al. 2006). It was also suggested that upregulation of cyclin D1 is a potential mechanism of resistance to novel anti-androgen agents (Pal et al. 2018). These findings suggest that CDK4&6 may play an important role in the development and/or progression of prostate cancer.

Preclinical studies in cell cultures and mouse xenograft prostate cancer models showed that single agent abemaciclib is effective in inducing cell cycle arrest and tumor growth inhibition (data on file). The clinical activity of abemaciclib in combination with abiraterone and prednisone is currently being investigated in I3Y-MC-JPCM (CYCLONE 2), a randomized, double-blind, placebo-controlled Phase 2 study in men with metastatic castration-resistant prostate cancer (mCRPC [NCT03706365]).

There is a high unmet medical need for mCRPC patients whose disease progressed after novel hormonal agent(s) (NHAs) and chemotherapy; thus, the development of tolerable and effective treatments with novel mechanisms of action is warranted. Study I3Y-MC-JPCY (CYCLONE 1) is an open-label single-arm, multi-center, Phase 2 study to evaluate the safety and efficacy of abemaciclib in this heavily pretreated mCRPC patient population.

2.2. Background

2.2.1. Prostate Cancer

Prostate cancer (PCa) is a leading cause of mortality and morbidity globally, with more than 1.2 million cases diagnosed and more than 359,000 deaths annually (Bray et al. 2018). It is the second most commonly diagnosed malignancy, the fifth leading cause of cancer mortality in men and represents a substantial public health burden (Bray et al. 2018). The majority of deaths from PCa are due to metastatic disease, identified either at diagnosis (de novo) or after relapse following local therapies.

Advanced PCa is an androgen-dependent disease and tumor cells are primarily dependent on AR activity for proliferation and survival. Thus, a standard element in the treatment of patients with metastatic disease is androgen deprivation therapy (ADT), which consists of bilateral orchiectomy or initiating a gonadotropin-releasing hormone agonist or antagonist (GnRHa) as monotherapy or in combination with an anti-androgen, also known as combined androgen blockade (Lonergan and Tindall 2011).

Based on the findings from the Phase 3 studies CHAARTED (NCT00309985), STAMPEDE (NCT00268476), and LATITUDE (NCT01715285), all showing significant improvement in overall survival (OS), the addition of docetaxel or abiraterone acetate plus prednisone to ADT is now considered a standard of care for men with high-volume or high-risk forms of metastatic hormone-sensitive prostate cancer (mHSPC) (Sweeney et al. 2015; James et al. 2016, 2017; Fizazi et al. 2019b). In addition, the ARCHES (NCT02677896) and ENZAMET (NCT02446405) studies with enzalutamide, and the TITAN (NCT02489318) study with apalutamide, recently demonstrated that addition of enzalutamide or apalutamide to ADT improves progression–free survival (PFS) in patients with mHSPC (Armstrong et al. 2019; Chi et al. 2018; Davis et al. 2019). Improvement of OS was also observed in ENZAMET and TITAN.

Advances in the management of non-metastatic castration-resistant prostate cancer (nmCRPC) have also been recently reported. The SPARTAN (NCT01946204), PROSPER (NCT02003924), and ARAMIS (NCT02200614) trials have demonstrated significant metastases-free survival benefit with apalutamide, enzalutamide or darolutamide, respectively, plus ADT in men with nmCRPC and whose prostate specific antigen (PSA) doubling time was 10 months or less (Hussain et al. 2018; Smith et al. 2018; Fizazi et al. 2019a).

Despite these significant advances, nearly all patients with mHSPC or nmCRPC experience disease progression to mCRPC and cancer-specific mortality. Overall, the median survival from mCRPC diagnosis is less than 2 years (Higano et al. 2019).

The therapies approved for the treatment of mCRPC (reviewed by Nuhn et al. 2019) include:

- Novel hormonal agents with abiraterone acetate (with prednisone) or enzalutamide,
- α-emitting radium isotope radium-223 (symptomatic bone metastases and no known visceral metastatic disease),
- Autologous cellular immunotherapy sipuleucel-T (asymptomatic or minimally symptomatic disease), and
- Taxane-based chemotherapy (docetaxel or cabazitaxel, with prednisone).

The optimum treatment sequence has not been established and the clinical activity of secondary NHAs (e.g. abiraterone after enzalutamide or the opposite sequence) is modest, likely due to cross resistance mechanisms (Noonan et al. 2013; Schrader et al. 2014; Smith et al. 2017). While chemotherapy is a standard approach in this setting, it is often associated with treatment-limiting toxicities.

Recently in the CARD study, treatment with cabazitaxel demonstrated statistically significant radiographic progression free survival (rPFS) benefit over anti-androgen therapy (abiraterone or enzalutamide) in participants with mCRPC who were previously treated with docetaxel and had progression within 12 months while receiving the alternative inhibitor (abiraterone or enzalutamide [de Wit et al. 2019]). The median rPFS was 8.0 months in the cabazitaxel group compared to 3.7 months in the anti-androgen group (hazard ratio 0.54; 95% confidence interval [CI], 0.40 to 0.73; p<.001). The median OS was 13.6 months in the cabazitaxel group compared to 11.0 months in the anti-androgen group (hazard ratio 0.64; 95% CI, 0.46 to 0.89; p=.008 [de Wit et al. 2019]). While these results support the use of cabazitaxel over abiraterone or enzalutamide in this setting, limited data exists to guide treatment for patients progressing after a NHA and taxane-based chemotherapy.

Among the current unmet needs in prostate cancer, the lack of therapeutic options for mCRPC patients who exhausted life prolonging therapies is one of the most pressing ones.

2.2.2. Abemaciclib

During the cell cycle, the G1 restriction point controls entry into the S phase and is essential for maintaining control of cell division (Sherr 1996; Ortega et al. 2002). The cyclin-dependent kinases (CDKs), CDK4 and CDK6 (CDK4&6), participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point by phosphorylating and inactivating the tumor-suppressor retinoblastoma protein (pRb). Alterations in this pathway occur frequently in human cancers and involve loss of CDK inhibitors by mutation or epigenetic silencing, mutation/overexpression of either CDK4 and CDK6 or cyclin D, or inactivation of *Rb*. These alterations may render cells less dependent on mitogenic signaling for proliferation. From a therapeutic standpoint, the goal of inhibiting CDK4&6 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− MBC.

Monotherapy with abemaciclib (200 mg, twice daily on a continuous dosing schedule) demonstrated meaningful antitumor activity in heavily pretreated refractory HR+, HER2− MBC patients with response rates of 19.7% and 28.6% observed in the single-arm Phase 2 study MONARCH 1 (NCT02102490) and in the randomized Phase 2 study Next MONARCH 1 (NCT02747004), respectively (Dickler et al. 2017; Hamilton et al. 2019).

In the randomized, placebo-controlled MONARCH 2 Phase 3 study, the addition of abemaciclib to fulvestrant provided a significant improvement of progression-free survival (PFS) (16.9 months versus 9.3 months, hazard ratio 0.536; 95% CI: 0.445, 0.645; p<.0001), OS (46.7 months versus 37.3 months, hazard ratio 0.757; 95% CI, 0.606-0.945; p=.01) and objective response rate (ORR) (measurable disease: 48.1% versus 21.3%; 95% CI: 42.6% to 53.6%;

p<.001) compared to placebo plus fulvestrant in HR+, HER2− advanced or metastatic BC patients who progressed during prior endocrine therapy (Sledge et al. 2017; Sledge et al. 2020). Of note, the OS benefit was consistent across subgroups including patients with a poorer prognosis with visceral metastases.

In the randomized, placebo-controlled MONARCH 3 Phase 3 study, the addition of abemaciclib to a nonsteroidal AI as initial treatment of HR+, HER2− advanced or MBC patients provided a significant improvement of PFS (28.2 months versus 14.8 months; hazard ratio 0.540; 95% CI: 0.418 to 0.698; p=.000002) and ORR (measurable disease: 61.0% versus 45.5%; p=.003) compared to placebo plus AI (Goetz et al. 2018; Johnston et al. 2019). The OS data, an important secondary end point of this study, are immature.

Abemaciclib is currently approved by major global regulatory authorities for the treatment of patients with HR+, HER2- advanced or MBC in combination with an AI as initial endocrine-based therapy and with fulvestrant following endocrine therapy. In addition, abemaciclib is also approved as monotherapy for heavily pre-treated (following endocrine therapy and chemotherapy) HR+, HER2- MBC patients by the FDA.

Using in vitro prostate cancer models, it has been shown that abemaciclib can inhibit pRb phosphorylation and arrest cells in G1 with evidence of subsequent senescence. In AR+ xenograft models, single agent abemaciclib dosed daily demonstrated significant antitumor activity. CCI [redacted] CCI [redacted] CCI [redacted] In these studies, single agent abemaciclib showed evidence of antitumor activity relative to the vehicle in each model and the abemaciclib plus enzalutamide arm demonstrated increased antitumor activity compared to both single-agent arms. Altogether, preclinical data suggests that abemaciclib monotherapy could exhibit clinical antitumor activity in prostate cancer.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of abemaciclib is to be found in the Investigator's Brochure (IB). Information on AEs expected to be related to abemaciclib may 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 standard of care endocrine therapies, such as GnRHa may be found in the respective Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

2.3.1. Benefit Assessment

There is a pressing unmet need for novel therapeutic agents in the care of mCRPC patients who experience disease progression following novel hormonal agent(s) (androgen-synthesis or receptor inhibitor, such as abiraterone acetate, apalutamide, darolutamide or enzalutamide and taxane-based chemotherapy with docetaxel and cabazitaxel. In this later-line setting, treatment options are limited and may include (where approved and if not previously given):

- An alternate novel hormonal agent (abiraterone or enzalutamide) - with possible acquired resistance and a potential limited benefit that needs to be considered.
- Radium-223 (for participants with symptomatic bone metastases, and no known visceral metastatic disease).
- Poly (ADP-ribose) polymerase inhibitors, such as rucaparib or olaparib, for a selected population (patients with homologous recombination repair gene mutations), per the respective approved labels.
- Agents which have shown some modest palliative benefits (such as mitoxantrone, corticosteroids, or other secondary hormone therapy, such as ketoconazole, diethylstilbesterol [DES], or other estrogens).
- Pembrolizumab in selected populations (patients with microsatellite instability -high or mismatch repair-deficient tumors) per the approved label.
- Clinical trials and best supportive care are additional options for these patients who have exhausted, or are not eligible to receive, life-prolonging therapies.

To the best of our knowledge, there are no historical control data for assessing treatment effects in this heavily pretreated patient population and clinical benefit obtained with treatment options mentioned above are likely to be of short duration.

In view of the potential antitumor activity of abemaciclib in the mCRPC population, CYCLONE 1 is designed to allow participants to continue therapy until disease progression. However, participants may discontinue study intervention at any time if they choose to do so or if the investigator believes it is in the best interest of the participant. Additionally, in the event of unacceptable toxicity, directions for reducing and/or discontinuing abemaciclib are provided. The assessment of patient-reported outcomes (PROs) will provide information on participants' experience of the treatment and will be part of the benefit-risk assessment.

This study is being performed to assess the safety and efficacy of abemaciclib monotherapy in participants with mCRPC whose disease progressed after at least 1 novel hormonal agent and 2 taxane-based chemotherapy regimens.

2.3.2. Overall Benefit: Risk Conclusion

Taking into account the safety profile of abemaciclib and the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with abemaciclib monotherapy are justified by the anticipated benefits that may be afforded to participants with heavily pre-treated mCRPC.

The benefit / risk assessment, therefore, currently favors the proposed abemaciclib study in participants who exhausted multiple or all life prolonging therapies for prostate cancer.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the efficacy of abemaciclib monotherapy.	• Investigator-assessed ORR per RECIST 1.1.
Secondary	
• To further characterize the clinical activity of abemaciclib monotherapy.	• rPFS • OS • DoR • DCR • PSA response rate • Time to PSA progression • Time to symptomatic progression
• To characterize the safety profile of abemaciclib.	• Assessment of safety including, but not limited to, the following: AEs, SAEs, physical examination, and clinical laboratory abnormalities per CTCAE v5.0
• To explore patient reported tolerability of abemaciclib monotherapy (including symptomatic AEs and overall side-effect burden), patient reported pain intensity, physical functioning, and overall health related quality of life	• PRO-CTCAE • FACT-GP5 • 7-day Worst Pain Numeric Rating Scale • EORTC QLQ-C30 Physical Functioning Scale • EORTC QLQ-C30 Global Health Status/QoL Scale
• To characterize the PK of abemaciclib and its metabolites.	• Concentrations of abemaciclib and its metabolites.
• To characterize Ki-67 baseline expression	• % of cells expressing Ki-67 by IHC
Exploratory	
CCI	

Objectives	Endpoints
CCI	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events v5.0 (NCI 2017); DCR = disease control rate; DoR = duration of response; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-GP5 = Functional Assessment of Cancer Therapy- General; IHC = immunohistochemistry; Ki-67 = protein encoded by the MKI67 gene; ORR= objective response rate; OS = overall survival; PK = pharmacokinetics; PSA = prostate specific antigen; PRO-CTCAE = Patient Reported Outcome-Common Terminology Criteria for Adverse Events v5.0 (NCI 2017); QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1 (Eisenhauer et al; 2009); rPFS = radiographic progression-free survival; SAE = serious adverse event; SSE = symptomatic skeletal event.

4. Study Design

4.1. Overall Design

CYCLONE 1 is a Phase 2 open-label, single-arm, multi-center study to assess the efficacy of abemaciclib monotherapy in participants with mCRPC whose disease progressed on or after at least 1 androgen-axis therapy (abiraterone acetate, apalutamide, darolutamide or enzalutamide) and 2 taxane-based chemotherapy regimens (docetaxel and cabazitaxel). Participants may have received up to 3 prior systemic treatments for mCRPC, must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and a metastatic lesion amenable to biopsy. Androgen deprivation therapy with a GnRHa must be continued throughout the study for participants who have not undergone bilateral orchiectomy. Abemaciclib 200 mg twice daily will be administered on a continuous dosing schedule until disease progression, unacceptable toxicity, or other discontinuation criteria are met.

This study will initially treat approximately 40 participants.

4.2. Scientific Rationale for Study Design

Patients whose mCRPC has progressed on or after prior NHA(s) and 2 taxane-based chemotherapy regimens represent a population with high unmet medical need.

In the recent CARD study (NCT02485691), treatment with cabazitaxel 25 mg/m^2 (with prednisone 10 mg daily and primary prophylactic granulocyte-colony stimulating factor [G-CSF] at every cycle) offered statistically significant rPFS benefit over anti-androgen therapy (abiraterone or enzalutamide) in participants with mCRPC who were previously treated with docetaxel and progressed within 12 months while receiving the alternative inhibitor (abiraterone or enzalutamide [de Wit et al. 2019]). The median rPFS was 8.0 months in the cabazitaxel group compared to 3.7 months in the anti-androgen group (hazard ratio 0.54; 95% CI, 0.40 to 0.73; p<.001). The principal reasons for the discontinuation of treatment with cabazitaxel or the anti-androgen therapy were disease progression (in 43.7% and 71.0% of the patients, respectively) or an AE (in 19.8% and 8.9% of the patients, respectively). The median OS was 13.6 months in the cabazitaxel group compared to 11.0 months in the anti-androgen group (hazard ratio 0.64; 95% CI, 0.46 to 0.89; p=.008 [de Wit et al. 2019]).

While these results support the use of cabazitaxel over a second NHA in this setting, as yet, there are limited data to guide treatment for mCRPC patients experiencing disease progression after receiving a NHA, docetaxel and cabazitaxel. This represents a high unmet medical need, as there was no standard of care for these patients. Of interest, in CARD, only about half (53.5%) of the patients in the cabazitaxel group received a subsequent anticancer treatment, 23.2% crossed over to receive a second hormonal agent (abiraterone or enzalutamide), 14.7% received palliative radiation, 4.7% received radium-223, 4.7% were enrolled in clinical trials to receive an investigational drug and 1.6% received docetaxel as re-challenge (de Wit et al. 2019).

The single arm, open label design for this study is justified as currently there are limited standard therapies with demonstrated activity for the study population.

Due to the nonoverlapping mechanism of action of abemaciclib when compared to currently approved therapies, and given its preclinical anti-proliferative effects on prostate cancer cell lines and xenograft models, the clinical activity and manageable safety profile as monotherapy observed in heavily treated HR+, HER2- MBC, abemaciclib may offer clinical benefit to the study population. This Phase 2 study will evaluate the safety and efficacy of abemaciclib monotherapy in the post-NHA(s) and post-chemotherapy mCRPC setting.

4.3. Justification for Dose

The maximum tolerated dose for abemaciclib monotherapy was defined in Phase 1 studies I3Y-MC-JPBA and I3Y-MC-JPBC (Japanese participants) as 200 mg every 12 hours, which demonstrated acceptable safety and tolerability in participants with solid cancers (Patnaik et al. 2016). Abemaciclib monotherapy is approved by the FDA for heavily pretreated HR+, HER2- MBC. The monotherapy indication is based on MONARCH 1 (NCT02102490) where abemaciclib 200 mg twice daily demonstrated a 19.7% (95% CI: 13.3, 27.5) ORR and median PFS of 6.0 months (Dickler et al. 2017).

CCI , in CYCLONE 1, abemaciclib monotherapy will be administered orally at 200 mg twice daily on Days 1 through 28 of a 28-day cycle.

4.4. End of Study Definition

This study will be considered complete (that is, scientific evaluation will be complete [study completion] following the evaluation of all primary and secondary endpoints, as determined by Lilly. Investigators will continue to follow the study schedule for all participants until notified by Lilly that study completion has occurred. "End of Study" refers to the date of the last visit or last scheduled procedure for the last participant.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria are met:

1. Adult male (age ≥18 years or country's legal age of majority), who must be, in the judgement of the investigator, an appropriate candidate for experimental therapy. Participants must be capable of giving signed informed consent as described in Section 10.1, Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Histologically confirmed adenocarcinoma of the prostate. Well-differentiated neuroendocrine carcinoma, small cell or large cell neuroendocrine carcinoma, sarcomatoid, and carcinoid tumors are excluded.

3. Metastatic prostate cancer documented by positive bone scan and/or computed tomography (CT) or magnetic resonance imaging (MRI). Presence of at least 1 measurable lesion per RECIST v1.1 (Eisenhauer et al. 2009). Previously irradiated lesions that did not show radiographic progression after radiation therapy, primary prostate lesion and bone lesions will be considered non-measurable disease. If lymph node metastasis is the only evidence of metastasis, it must be at least 1.5 cm in the short axis.

4. Serum testosterone ≤1.73 nmol/L (≤50 ng/dL) at the screening visit. Participants who have not undergone bilateral orchiectomy are required to continue ADT with a GnRHa throughout the study.

5. Progressive disease despite castrate level of serum testosterone based on at least 1 of the following criteria:
    - Prostate specific antigen (PSA) progression per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria for trial eligibility: A sequence of at least 2 rising PSA values at a minimum of 1-week intervals, with the last value being at least 1.0 ng/mL.
    - Radiographic progression per RECIST v1.1 for soft tissue and/or per PCWG3 for bone (appearance of ≥2 new bone lesions on bone scan), with or without PSA progression.

6. Participants must have previously received in the metastatic hormone-sensitive setting and/or in the castration-resistant settings:
    - At least 1 novel androgen receptor-axis therapy with abiraterone acetate, apalutamide, darolutamide or enzalutamide

    AND
    - 2 taxane regimens. A taxane regimen is defined as at least 2 cycles of docetaxel or cabazitaxel. Re-challenge with docetaxel will not be considered a second taxane regimen.

    If a participant has not received a second taxane regimen, the participant may still be eligible after discussion and approval by the Lilly clinical research physician/scientist (CRP/CRS) if:
    - Participant has history of hypersensitivity reactions or intolerance to docetaxel, cabazitaxel, drugs formulated with polysorbate 80 or to corticosteroids
      or
    - Participant has any contraindication or preexisting condition not compatible with receiving an additional taxane therapy per local prescribing information
      or
    - Participant experienced taxane-related AE requiring treatment discontinuation or did not yet resolve to Grade ≤1 (except alopecia).

    The reason must be recorded in the participant's medical notes and medical history in the electronic case report form (eCRF).

7. Participants may have received up to 3 prior systemic therapy regimens in the metastatic castration-resistant setting.
   NOTE: GnRHa, first-generation antiandrogens (flutamide, nilutamide, or bicalutamide), DES (or other estrogens), corticosteroids, ketoconazole, and bone loss-prevention will not count as systemic therapy regimens.

8. Except for GnRHa and bone loss-prevention treatment, participants must have discontinued previous anti-cancer agents at least 21 days (or 5 half-lives, whichever is shorter) prior to treatment initiation. Participants must have recovered from acute toxic effects of prior therapy, palliative radiation or surgical procedure to Grade ≤1 or baseline (as per Common Terminology Criteria for Adverse Events [CTCAE] v 5.0), with the exception of alopecia or peripheral neuropathy.

9. Must be willing and amenable to undergo tumor biopsy of at least 1 metastatic site, which should be collected following determination of eligibility and before initiating study treatment.
    - Soft tissue biopsy is strongly preferred to bone biopsy whenever possible.

- Biopsy of newly emerged radiographic metastases preferred to biopsy of previously existing lesions whenever possible.
- Adequate archival metastatic tissue can be used if available in lieu of a new biopsy if the biopsy was done within 12 weeks prior to enrollment and no treatment was initiated from biopsy to study entry.

10. Have Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 (Oken et al. 1982) and adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	$\geq 1.5 \times 10^9$/L G-CSF should not be administered to meet ANC eligibility criteria.
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥9 g/dL Participants may receive erythrocyte transfusion to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.
Hepatic	
Total bilirubin	≤1.5 × ULN OR <2.0 × ULN for participants with history of unconjugated hyperbilirubinemia (Gilbert's syndrome)
ALT and AST	≤ 3 ×ULN

Abbreviations: ALT = alanine transaminase; ANC= absolute neutrophil count; AST = aspartate transaminase; dL = deciliter; G-CSF = granulocyte-colony-stimulating factor; g = gram; L= liter; ULN= upper limit of normal.

11. Sexually active participants, with a female partner who is of child-bearing potential, must agree to use a medically approved contraceptive method during the study and for at least 3 weeks following the last dose of abemaciclib (e.g., intrauterine device, nonhormonal birth control pills, or barrier method). If condoms are used as a barrier contraceptive, a spermicidal agent should be added as double barrier protection. Please refer to Section 10.4, Appendix 4, for additional reproductive and contraceptive guidance.

5.2. Exclusion Criteria

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

12. Prior treatment with abemaciclib or any CDK4 and/or CDK6 inhibitors.

13. Currently enrolled 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 unless agreed by the Lilly CRP/CRS. If a participant 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.

14. Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of any origin), unless in complete remission with no therapy for a minimum of 2 years.

15. Serious and/or uncontrolled preexisting medical condition(s) including but not limited to severe renal impairment (for example, estimated creatinine clearance <30 mL/min), severe hepatic impairment (Child-Pugh C), interstitial lung disease (ILD)/pneumonitis, severe dyspnea at rest or requiring oxygen therapy. Other serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis, preexisting chronic condition resulting in Grade ≥2 diarrhea, gastrointestinal disorder affecting absorption or inability to swallow medication).

16. History of any of the following conditions within the last 12 months: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.

17. The participant has 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.

18. Known or suspected central nervous system (CNS) metastatic disease (baseline screening for CNS metastases is not required unless there is presence of signs and/or symptoms of CNS involvement).

19. Untreated spinal cord compression or evidence of spinal metastases with risk of spinal compression. Structurally unstable bone lesions suggesting impending fracture.

20. Estimated life expectancy < 4 months as assessed by the investigator.

5.3. Lifestyle Considerations

- Participants should refrain from consuming grapefruits or grapefruit juice while on study intervention.
- Participants must not take preparations or herbal products thought to affect PSA levels (such as, saw palmetto or pomegranate).
- Participants must not donate blood or sperm during the study and for 3 months after the last study intervention dose.
- Participants with known hypersensitivity or suspected intolerance to abemaciclib or any of its excipients (e.g., lactose) should not take abemaciclib unless deemed appropriate by the investigator.

See Section 6.5 for additional guidance on concomitant therapy.

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 SAEs.

The following participants may be eligible for re-screening:

- Participants who become eligible to enroll in the study as a result 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 (e.g., 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. The individual 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.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. In CYCLONE 1, study intervention is defined as the administration of abemaciclib.

6.1. Study Intervention(s) Administered

Abemaciclib will be administered at a starting dose of 200 mg orally twice daily with a minimum of 6 hours between doses, at approximately the same time every day. Abemaciclib 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). Abemaciclib 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 and then twice-daily administration should be resumed (with at least 6 hours separating doses). 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.

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

- Explaining the correct use of the drug and planned duration of each individual's treatment to the participant/study-site personnel/legal representative.
- Verifying the instructions are followed properly.
- Maintaining accurate records of abemaciclib dispensing and collection.
- Returning all unused medication to Lilly, or its designee at the end of the study, unless the site is authorized by Lilly or its designee to destroy unused medication, as allowed by local law.

Study Intervention	Dose	Treatment Schedule	Route of Administration
Abemaciclib	200 mg	Twice daily	Oral

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature/storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized study personnel may supply study intervention. All study intervention 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.

The investigator, or authorized study personnel, is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

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

6.2.1. Selection and Timing of Doses

A treatment cycle is defined as an interval of 28 days. Abemaciclib will be administered orally twice daily at approximately the same times each day on Days 1 through 28 of a 28-day cycle (±3 days). 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 cycle delay or earlier start due to logistical reasons (for example, due to holiday, 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). In exceptional cases, such as planned delays (including but not limited to vacation or holidays), additional study treatment may be dispensed after discussion with Lilly CRP/CRS.

Participants may continue to receive study intervention until evidence of disease progression, or any discontinuation criteria are met (See Section 7).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a non-randomized, open-label study.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each cycle. Compliance will be assessed by counting returned tablets. Study medication administration data will be recorded in the participant's medical record and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Participants who are significantly noncompliant will be discontinued from the study after discussion with Lilly CRP/CRS. A participant will be considered significantly noncompliant if he missed more than 7 consecutive days of study medication (full dose) or more than 25% cumulative days of study medication (full dose). Similarly, a participant may be considered significantly noncompliant if he is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Abemaciclib dose suspensions or delays related to toxicity may occur and will not result in a participant being considered noncompliant.

6.5. 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 eCRF. 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. Refer to the prescribing information of the concomitant medications for additional information.

Required:

Participants who have not undergone bilateral orchiectomy are required to continue ADT with a GnRHa throughout the study. The choice of the GnRHa will be at the investigator's discretion.

Permitted:

Bone loss prevention treatment with bisphosphonates or denosumab per their respective approved labels. Switching between bisphosphonates and denosumab is permitted during study as long as it is in the absence of disease progression, and due to reasons including, but not limited to, tolerability.

Use with Caution:

Abemaciclib is extensively metabolized through oxidation by cytochrome P450 (CYP)3A. In clinical drug interaction studies,

- coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure 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 10.6, Appendix 6). This includes grapefruit or grapefruit juice. In particular, avoid oral administration of the very strong CYP3A inhibitor, ketoconazole. The information in Section 10.6, Appendix 6, is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of abemaciclib by 50 mg at the start of CYP3A inhibitor treatment. That is, for patients receiving 200 mg twice daily, reduce the dose to 150 mg twice daily. For patients who have already dose reduced to 150 mg or 100 mg twice daily for tolerability, reduce the dose further to 100 mg or 50 mg twice daily, respectively. Alternatively, the investigators may consider suspending abemaciclib 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 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 dose requires review and approval from Lilly CRP/CRS. Inducers of CYP3A should be substituted or avoided if possible (Section 10.6, Appendix 6). Coadministration with a CYP3A inducer ≥28 days must be discussed with Lilly CRP/CRS.

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.

Prohibited:

With the exception of a GnRHa, no other anticancer therapy 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, anti-cancer vaccines, ketoconazole).

Palliative radiation or surgical intervention to treat symptoms resulting from metastatic disease is not allowed.

Drugs, or herbal/non-herbal products (e.g., 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. Megestrol acetate as an appetite stimulant is not permitted.

6.5.1. Supportive Care

Participants should receive full supportive care to maximize quality of life. Participants will receive supportive care as judged by the treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult with the Lilly CRP/CRS. Use of any supportive care should be recorded on the eCRF.

6.5.1.1. Supportive Management for Diarrhea

When abemaciclib is initiated, the participant should receive instructions on 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 participant should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Participants should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids 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, abemaciclib should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences dosing should be adjusted as outlined in Section 6.6.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics, such as fluoroquinolones must be prescribed.

Participants 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.

Refer to Section 6.6 for guidance on dose adjustments of abemaciclib for patients with diarrhea and see Section 10.7, Appendix 7, for diarrhea CTCAE grades.

6.5.1.2. Growth Factors

Growth factors should not be administered to a participant to satisfy study inclusion criteria.

While on study treatment, growth factors may be administered in accordance with American Society of Clinical Oncology guidelines (Smith et al. 2015). Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced by 1 dose level on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

6.6. 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 abemaciclib per investigator judgment). The CTCAE v5.0 will be used to assess AEs. Abemaciclib may be suspended for a maximum of 28 days to allow a participant sufficient time for recovery from abemaciclib-related toxicity. If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient should be considered for permanent discontinuation from abemaciclib. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the Lilly CRP/CRS.

Participants undergoing non-tumor related 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 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. The scars should be aseptic and healing process be reasonable before resuming abemaciclib.

Dose reductions for abemaciclib should be performed as shown in the table below. Abemaciclib must be reduced sequentially by 1 dose level, unless an exception is granted in consultation with the Lilly CRP/CRS. For participants requiring a dose reduction of study intervention, any re-escalation to a prior dose level is permitted only after consultation with and approval by the Lilly CRP/CRS.

6.6.1. Dose Reductions for Abemaciclib

Study Drug	Starting dose	Dose Reduction			
		First	Second	Third	Fourth
Abemaciclib	200 mg twice daily	150 mg twice daily	100 mg twice daily	50 mg twice daily	Discontinue

6.6.2. Dose Adjustments and Delays Abemaciclib

The toxicity dose adjustments and delays table below provides guidance for the management of treatment-emergent, related (i.e., with reasonable causal relationship with abemaciclib), and clinically significant AEs associated with abemaciclib. An investigator may suspend or reduce doses without meeting one of the criteria below and would not be considered a protocol deviation.

Toxicity Dose Adjustments and Delays of Abemaciclib

Toxicity Type	CTCAE Grade	Dose Modification
Hematologic Toxicity	Grade 1 or Grade 2	No dose modification is required
	Grade 3	Suspend dose until toxicity resolves to ≤Grade 2 Dose reduction is not required
	Recurrent Grade 3, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2 Resume at next lower dose level
Hematologic Toxicity: If Patient Requires Administration of Blood Cell Growth Factors Additional guidance for use of growth factors is in Section 6.5.1.2	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Suspend dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2 Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor
Non-hematologic Toxicity Excluding Diarrhea, ALT/AST Increased, and Interstitial Lung Disease/Pneumonitis (see below) Additional guidance for renal monitoring is in Section 8.2.2.2 and for venous thromboembolic events is in Section 8.2.2.3	Grade 1 or Grade 2	No dose modification is required
	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1. Grade 3 or Grade 4	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose level
Diarrhea Additional guidance for diarrhea management is in Section 6.5.1.1. See Section 10.7, Appendix 7, for CTCAE 5.0 grading	Grade 1	No dose modification is required
	Grade 2 that does not resolve within 24 hours to ≤Grade 1	Suspend dose until toxicity resolves to ≤Grade 1 Dose reduction is not required
	Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures.	Suspend dose until toxicity resolves to ≤Grade 1 Resume at next lower dose level

Toxicity Type	CTCAE Grade	Dose Modification
	Grade 3, or Grade 4, or requires hospitalization	
ALT/AST Increased See Section 8.2.2.1 for additional guidance for hepatic monitoring and Section 8.2.2.1.1 for special hepatic safety data collection. See Section 10.7, Appendix 7, for CTCAE 5.0 grading	Grade 1 or Grade 2	No dose modification is required
	Persistent or recurrent Grade 2, or Grade 3	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose
	≥Grade 2 with total bilirubin >2× ULN, in the absence of cholestasis, or Grade 4	Discontinue abemaciclib
Interstitial Lung Disease/Pneumonitis Additional guidance for ILD/pneumonitis monitoring is in Section 8.2.2.4. See Section 10.7, Appendix 7, for CTCAE 5.0 grading	Grade 1 or Grade 2	No dose modification is required
	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days.	Suspend dose until toxicity resolves to baseline or Grade ≤1 Resume at next lower dose level
	Grade 3 or Grade 4	Discontinue abemaciclib

Abbreviations: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ILD = interstitial lung disease; ULN = upper limit of normal.

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 drug 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.

6.7. Intervention after the End of the Study

Please refer to the study schema (Section 1.2) for a depiction of study completion, continued access period, and the end of study.

6.7.1. Study Completion

Study completion will occur following the final analysis of all primary and secondary objectives (Section 4.4), as determined by Lilly. Investigators will continue to follow the SoA (Section 1.3) for all participants until notified by Lilly that study completion has occurred.

6.7.2. Continued Access

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.

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.

The participant's continued access to study intervention will end when a criterion for discontinuation is met (Section 7). 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.

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.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants may discontinue the study intervention at any time for any reason. Investigators should try to find out the reason and document it on the corresponding CRF.

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

Participants with PSA-only progression should continue study intervention until disease progression (radiographic and/or symptomatic progression), when participant safety is not compromised.

Study intervention should be continued for as long as the participant consents and complies with study procedures and requirements, is tolerating the study intervention, until radiographic progression according to RECIST 1.1 for soft tissue and/or PCWG3 for bone; and/or until symptomatic progression.

Symptomatic progression is defined as:

- Symptomatic Skeletal Event (SSE), defined as 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 anti-cancer therapy.
- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

When study intervention is discontinued due to symptomatic progression, the investigator should obtain CT/MRI and bone scan imaging within 14 days to assess for radiographic progression, prior to the participant initiating radiotherapy, surgery or subsequent anti-cancer therapy (whichever comes first).

Patients discontinuing study intervention due to documented radiographic progression will be followed for the development of symptomatic progression until start of new anticancer therapy, withdrawal of consent, death, or study completion, whichever occurs first.

Participants discontinuing study intervention prior to documented radiographic progression will continue to have scheduled disease assessments until documented radiographic progression, start of new anticancer therapy, withdrawal of consent, death, or study completion, whichever occurs first.

All participants discontinuing study intervention will have procedures performed as shown in Section 1.3 and enter the short-and-long-term follow-up periods and will be followed for the initiation of subsequent anti-cancer therapies and survival status every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first.

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

- the participant or the participant's designee (for example, parents or legal guardian) requests to be discontinued from study intervention
- sponsor decision
- investigator decision
- the participant is enrolled in any other clinical trial involving an investigational product or other type of medical research judged not to be scientifically or medically compatible with this study
- radiographic or symptomatic disease progression as discussed above
- the participant, for any reason, requires treatment from another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study intervention will occur prior to introduction of the new agent.
- the participant experiences unacceptable toxicity
- the participant is significantly noncompliant with study procedures and/or intervention.

In exceptional circumstances, a participant may continue study intervention beyond disease progression if there is no effective alternative therapy and 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 patient to continue study intervention. Additionally, the patient 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:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- 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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). The participant will be permanently discontinued both from the study intervention and from the study at that time.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

The criteria for enrollment must be followed explicitly. If an inadvertently enrolled participant is identified, the sponsor and investigator must be notified. A discussion must occur between the Lilly CRP/CRS and the investigator to determine if the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may continue in the study and on study drug when the Lilly CRP/CRS agrees with the investigator that it is medically appropriate for that patient to do so. The patient may not continue in the study with or without study drug if the Lilly CRP/CRS does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study drug. Patients who are discontinued from the study will have follow-up procedures

performed as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

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 who initiate treatment. 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 summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. 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 may 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.

The SoA (Section 1.3) provides the schedule for collection of samples in 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

Baseline and on-study tumor assessments will be performed for each participant as per the SoA (Section 1.3), according to the calendar days, regardless of intervention delays. During the study, unscheduled tumor assessment and appropriate imaging should be considered if there are signs or symptoms suggestive of disease progression.

All applicable imaging will be done locally. All CT/MRI and bone scan images will be collected and stored centrally.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST 1.1.

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

For participants continuing treatment during the Continued Access Period (after study completion), efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator.

8.1.1. Definitions of Efficacy Measures

Objective Response Rate is defined as the proportion of participants who have a soft tissue best overall response of complete response (CR) or partial response (PR) per RECIST 1.1, and do not have concurrent bone disease progression per PCWG3, as assessed by the investigator/local

radiologist. The primary analysis will require confirmation of responses, but interim analyses will consider both confirmed and unconfirmed responses.

Radiographic Progression Free Survival

The consensus guidelines of RECIST 1.1 and PCWG3 have been taken into consideration for the determination of radiographic disease progression.

For all participants, imaging studies (radionuclide bone scan and CT or MRI scan of the chest, abdomen, and pelvis) will be performed locally at baseline and repeated within 7 days prior to Day 1 of every second cycle (every 8 weeks) beginning with Cycle 3 and continuing until radiographic progression, and within 14 days of symptomatic progression if no radiographic progression yet per the SoA (Section 1.3).

Radiographic PFS (rPFS) will be assessed by sequential imaging studies and is defined as the time from the date of treatment initiation to the earliest date of investigator-determined radiographic disease progression by objective radiographic CT/MRI disease assessment per RECIST 1.1 for soft tissue AND/OR radionuclide bone scan using the PCWG3 criteria for bone or death from any cause, in the absence of documented disease progression. Censoring rules are described in detail in the Statistical Analysis Plan (SAP). Radiographic disease progression in soft tissue does not require a confirmatory scan.

The documentation required for the determination of radiographic disease progression in bone per PCWG3 is listed in the text below and in the following table.

Bone Progression per PCWG3

A participant is considered to have progressed by bone scan if:

1. For radiographic disease progression on bone observed on the first post-treatment bone scan
   - Appearance of at least 2 new lesions on the first post-treatment scan (Week 9), with at least 2 additional lesions on the next scan (Week 17; 2+2 rule).
   - The date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented.

OR

2. For radiographic disease progression in bone observed after the first post-treatment bone scan (Week 17 or later):
   - Appearance of at least 2 new lesions relative to the first post-treatment scan (Week 9, new baseline) that are persisting on a confirmatory subsequent scan (at least 6 weeks later or at the next scheduled assessment).
   - The date of progression is the date of the scan that first documents the second lesion.

Changes in intensity of uptake alone do not constitute either progression or regression.

Date Progression Detected	Criteria for Progression	Criteria for Confirmation or Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Subsequent Scan
Week 9 (C3D1) (or earlier unscheduled visit)	Two or more new lesions compared to baseline bone scan	Requires confirmation at least 6 weeks after progression identified or at the Week 17 assessment	Confirmatory scan: Two or more new bone lesions compared to Week 9 scan
Week 17 or later	Two or more new lesions on bone scan compared to Week 9 bone scan	Requires confirmation at least 6 weeks after progression identified or at the next scheduled assessment	Confirmatory scan: Two or more persisting (i.e., also present on the prior scan) new lesions relative to Week 9 scan

Abbreviations: C = cycle; D = day.

Source: Scher et al. 2016.

Overall Survival is defined as the time from the date of treatment initiation to date of death due to any cause. For participants not known to have died at the time of analysis, OS will be censored at the last known alive date.

Duration of Response is defined as the time from first documented evidence of soft tissue CR or PR until earliest date of disease progression by objective radiographic disease assessment per RECIST 1.1 for soft tissue AND/OR radionuclide bone scan using PCWG3 criteria for bone as assessed by the investigator/local radiologist, or death from any cause, whichever occurs first.

Disease Control Rate is defined as the proportion of patients who have a soft tissue best overall response of CR, PR, or stable disease (SD) per RECIST 1.1, and do not have concurrent bone disease progression per PCWG3.

Time to PSA progression is defined as the time from the date of treatment initiation 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 smallest 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 (Scher et al. 2016).

Time to Symptomatic Progression is defined as the time from the date of treatment initiation to any of the following (whichever occurs earlier):

- Symptomatic Skeletal Event (SSE), defined as symptomatic pathological fracture, tumor-related orthopedic surgery, or external beam radiation to bone progression, or spinal cord compression.
- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy.

- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

Prostate Specific Antigen Response Rate is defined as the proportion of participants with a reduction in PSA level of ≥50% from baseline (see Section 9.4.1), confirmed with a second assessment conducted at least 3 weeks later.

PSA Change from Baseline to 13 Weeks is defined as the individual proportion of rise or fall in PSA at 13 weeks relative to baseline (see Section 9.4.4). Missing observations will not be imputed.

Maximum Decline in PSA is defined as the relative change in PSA from baseline (see Section 9.4.1) to the lowest on-study value, occurring at any time point.

8.1.2. Appropriateness of Assessments

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology studies.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). For each participant, vital signs, laboratory tests, and other tests should be collected as shown in the SoA.

Any clinically significant findings that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to Lilly or its designee as an AE via eCRF.

Additional information regarding guidance for monitoring of hepatic function, renal function, venous thromboembolic events (VTE), and interstitial lung disease (ILD)/pneumonitis can be found in Section 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments

Lilly or its designee will provide the investigator with the results of safety laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

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

The investigator must review laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or until the completion of Visit 801 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- 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 laboratory manual SoA.
- If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE, AE, or dose modification), then the results should be reported as a diagnosis of an AE (for example, hypertension, neutropenia, etc.).

8.2.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

8.2.2.1. Hepatic Safety Monitoring

Liver testing (Section 10.5, Appendix 5), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine phosphokinase, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one 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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

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-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time-international normalized ratio; 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 designated medical monitor, 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 serum 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.

8.2.2.1.1. Special Hepatic Safety Data Collection

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

In participants 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 intervention due to a hepatic event or abnormality of liver tests
- occurrence of a hepatic event considered to be an SAE

8.2.2.2. 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 (GFR) 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 GFR, should be used as an alternative to either creatinine or creatinine calculations of GFR. A serum cystatin C is collected with the central chemistry laboratory sample. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities in Section 6.6.2.

8.2.2.3. Guidance for Venous Thromboembolic Events

In breast cancer, VTE has been identified as an adverse drug reaction for abemaciclib in combination with endocrine therapy (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 particular 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 should follow the protocol guidance for non-hematological toxicities in Section 6.6.2.

8.2.2.4. Guidance for Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis has been identified as an adverse drug reaction 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.

Ask your participants to report any new or worsening pulmonary symptoms, such as dyspnea, cough, and fever, and investigate and treat as per your 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 6.6.2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Section 10.7, Appendix 7, for ILD/pneumonitis CTCAE grades). Discontinue abemaciclib in cases of severe (Grade 3 or 4) ILD/pneumonitis.

8.2.3. Safety Surveillance

The sponsor has robust safety surveillance processes based on recommendation made by Council for International Organizations of Medical Sciences (CIOMS) Working Group VI - Management of Safety Information from Clinical Trials Report. These processes are in line with FDA's expectations for Safety Assessment Committees and the European Medical Agency (EMA) expectations for monitoring safety in clinical trials.

Each investigational drug has a Developmental Safety Surveillance Team (DSST) which is responsible for monitoring the safety of participants and overseeing the evolving safety profile of investigational drugs. The DSST will review all available data including but not limited to clinical trial data (cumulative AE and SAE data and laboratory data), non-clinical data (toxicology studies), epidemiology studies and literature. The team will conduct real time review of all SAEs and other incoming expedited safety reports. The DSST is also responsible for review of accumulating safety data across all trials for the investigational drug. The DSST will meet in a timely manner at pre-defined intervals or on an ad-hoc basis as required.

The DSST is a multidisciplinary team which includes a physician/scientist who are well versed in Pharmacovigilance and with the therapeutic area for which the investigational drug is being developed. The roles and responsibilities of this team and the processes are clearly defined in Lilly's internal Standard Operating Procedures.

Each investigational drug has a Developmental Safety Management Team (DSMT) which is a cross-functional, multidisciplinary team and includes DSST members, study team physicians and other members depending on the necessity such as epidemiologist, clinical pharmacologist, toxicologist, statistician. The DSST and DSMT work together to review clinical data from the clinical trial.

The DSST can make recommendations to the DSMT in order to minimize risk to participants in clinical trials. Such recommendations will include (but are not limited to) changes to conduct of the trial, determination of new adverse drug reactions and determining if event(s) meets the criteria for expedited reporting to regulators (such as investigational new drug [IND] safety reports) and investigators.

In addition, each individual clinical trial study team has clearly defined processes to review all relevant safety data at cohort level and trial level in order to monitor safety of participants in clinical trials and enable trial level decisions such as dose escalation. More information about these processes can be found in Section 6.6 of the protocol.

Lilly Global Patient Safety has a robust process, for expedited communication of SAEs and suspected unexpected serious adverse reactions (SUSARs) per regulatory requirements and other important study information as needed. The protocol gives detailed information to study sites for collection and reporting of AEs and SAEs (see Sections 8.3 and 10.3, Appendix 3).

8.3. Adverse Events and Serious Adverse Events

Lilly standards for reporting AEs are to be followed regardless if 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 considered related to abemaciclib.

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 the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or 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.

Investigators are responsible for:

- monitoring the safety of participants in this study and for alerting Lillyor its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant
- the appropriate medical care of participants during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study intervention or the study, or that caused the participant to discontinue study intervention before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

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 participant'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. Time Period and Frequency for Collecting AE and SAE Information

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.

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.

8.3.2.1. 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 10.4, Appendix 4, for details.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) 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 a 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 a 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.

8.3.5. Pregnancy

Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until 3 weeks following cessation of study intervention.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.3, Appendix 3.

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

8.3.6. Adverse Events of Special Interest

More information about the adverse events of special interest for abemaciclib can be found in the IB.

8.3.7. Complaint Handling

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 trial intervention.

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he has a complaint or problem with the investigational product so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Sections 8.3.3 and 10.3, Appendix 10.3, of the protocol.

8.4. Treatment of Overdose

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 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.

8.5. Pharmacokinetics

Pharmacokinetic samples will be collected to determine the concentrations of abemaciclib and its active metabolites, LSN3106726 (M20) and LSN2839567 (M2). Blood samples for PK analysis will be collected by

1) venous puncture collection into a vacutainer, and
2) capillary puncture collection into a volumetric absorptive microsampling device.

At the visits and times specified in the SoA (Section 1.3.1), both a venous blood sample and a blood microsample should be collected at approximately the same time (within [+/-] 10 minutes)

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 will be retained for a maximum of 1 year following last subject visit for the study.

A maximum of 3 samples may be collected at additional time points 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.

8.5.1. Patient Diary

A diary will be provided to participants in order to help track date and time of each dose taken the day before planned PK sample collection. Patient diary evaluations will occur through Cycle 3 Day 1. Refer to SoA (Section 1.3) for additional information.

8.6. Pharmacodynamics

See Section 8.8. Samples collected will be identified by the participant number (coded) and retained at a facility selected by Lilly for a maximum of 15 years following the last participant visit for the study.

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

CCI

8.8. Biomarkers

8.8.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 8.8. The following tissue samples for biomarker research will be collected according to Section 1.3.1, where local regulations allow.

Collection of the following tumor tissue sample(s) is **required** for all participants in order to participate in this study:

- Mandatory tumor biopsy of at least 1 metastatic site which will be collected following determination of eligibility and before initiating study intervention.
    - Biopsy of newly emerged radiographic metastases is preferable to the biopsy of previously existing lesions whenever possible.
    - Soft-tissue, as well as bony metastatic lesions will be considered acceptable. Soft-tissue biopsy is preferred to bone biopsy whenever possible.

At the time of tissue collection, it is highly recommended to confirm adequate tumor tissue (not a normal adjacent tissue sample or a tumor margin sample) has been sampled.

Adequate archival metastatic tissue can be used if available in lieu of a new biopsy if the biopsy was done within 12 weeks prior to enrollment AND no treatment was initiated from biopsy to study entry. Sites should confirm availability of archival tissue with pathology laboratory prior to study entry.

An optional biopsy of metastatic lesion at the time of radiographic progression should only be considered if the participant has completed at least 4 cycles of study intervention. The biopsy of a newly emerged or a progressing metastasis is preferred over a pre-existing lesion that is not progressing, whenever possible.

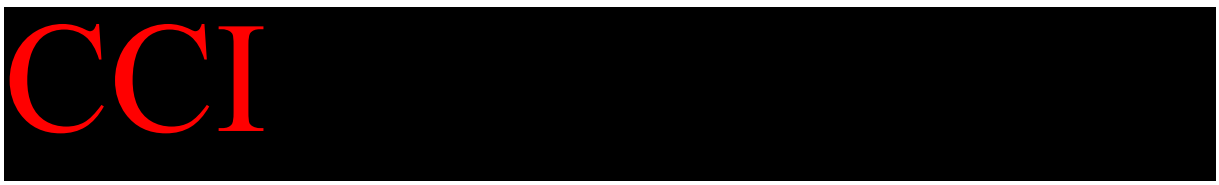
The pathology report accompanying archival tissue may also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Lilly has a right to retain a portion of the submitted tissue.

Archival blocks will be sectioned and returned to study site upon request. Slides and tumor tissue samples collected as part of this study will not be returned.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables the use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later.

Technologies are expected to improve during the 15-year storage period, and therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

8.8.2. Other Samples for Biomarker Research



8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics

8.10.1. Patient reported outcomes

The main objective of the patient reported outcome (PRO) measurement is to assess patient reported tolerability (i.e., assessment of symptomatic AEs). In addition, the measurement of PROs will focus on the overall side effect impact, disease related symptoms, specifically pain, and well as physical functioning and global health related quality of life.

Patient reported symptomatic AEs will be measured using The National Cancer Institute's PRO version of the common terminology criteria for adverse events (PRO-CTCAE) (http://healthcaredelivery.cancer.gov/pro-ctcae/). The choice of PRO-CTCAE symptoms items selected from the PRO-CTCAE item library is aligned with the recommendations published in Trask et al. 2018. CCI [redacted] Additionally, the GP5 item of the Functional Assessment of Cancer Therapy-General (FACT-G) instrument, which asks participants to report the extent to which "(they are) bothered by side-effects of treatment", will be administered to assess overall side-effect burden.

The impact of abemaciclib on pain will also be explored using the 7-day Worst Pain Numeric Rating Scale (NRS) data and analgesic use. The 7-day Worst Pain NRS is a single-item questionnaire which measures worst pain over the last 7 days on a 0 to 10 point numeric rating scale, where 0 is 'no pain' and 10 is 'pain as bad as you can imagine'. Data on over-the-counter and prescription analgesic medications including dose, unit, frequency, and route of administration will be collected by site personnel and recorded in the CRF. Analgesic use will be classified into categories, for example, according to the World Health Organization analgesic ladder or the Analgesic Quantification Algorithm scale.

Physical functioning and overall health-related quality of life will be measured using the Physical Functioning and Global Health Status/ Quality of Life (QoL) scales of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLC-C30). Both the GP5 item and EORTC QLQ-C30 items are measured on a 5-point Likert scale, from 'not at all' to 'very much'.

The PRO-CTCAE, FACT-GP5, 7-day Worst Pain NRS, and EORTC QLQ-C30 Physical Functioning and Global Health Status/QoL scales will be administered at baseline (screening), Day 1 of every cycle, treatment discontinuation, and short-term follow-up. Questionnaires should be completed by all participants where there is a validated language/cultural translation available in which the patient is fluent. The questionnaires should be completed before any extensive contact and consultation with the clinician/study investigator, as such encounters may thereafter bias patient responses. Questionnaires should be administered in the following order: 7-day Worst Pain NRS, then PRO-CTCAE, then FACT-GP5, and finally the QLQ-C30 Physical Functioning and Global Health Status/QoL scales.

8.10.2. Health Care Resource Utilization

Health care resources utilization data, associated with medical encounters, will be collected in the eCRF by the investigator or authorized study personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct economic analyses and will include hospitalizations and emergency room visits (reason and duration).

9. Statistical Considerations

9.1. Statistical Hypotheses

The statistical hypothesis of this study is that there will be a clinically relevant rate of response to abemaciclib monotherapy administered to patients with mCRPC that have been previously treated with at least 1 novel androgen-axis therapy (androgen-synthesis or receptor inhibitor, such as abiraterone acetate, apalutamide, darolutamide or enzalutamide) and 2 taxane regimens (docetaxel, cabazitaxel).

9.2. Sample Size Determination

Approximately 40 participants will be assigned to study intervention. All treated patients will be included in the assessment of objective response, with patients lacking a complete disease assessment per RECIST 1.1 criteria at either baseline or at any time postbaseline being classified as non-responders.

An observed response rate of at least 12.5% in 40 participants will be considered as evidence of clinically relevant activity, which yields an adequate Type I error rate and power. As an illustration of Type I error control, assuming a true response rate of 5%, the probability of observing an ORR of at least 12.5% in a cohort of 40 participants is 4.8%. As an illustration of power, assuming a true response rate of 15%, the probability of observing an ORR of at least 12.5% is 73.7%.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF
Treated/Safety	All participants who have initiated study intervention, regardless of how many doses of study intervention they receive or how many on-study research procedures are performed.
Biomarker Evaluable	All participants within the subset of participants from the Treated population from whom a valid pre-treatment tumor assay result has been obtained.
Pharmacokinetic Analysis	All treated participants who received at least 1 dose of abemaciclib and have at least 1 evaluable PK sample.

Abbreviations: ICF = informed consent form; PK = pharmacokinetics.

9.4. Statistical Analyses

9.4.1. General considerations

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

This is an uncontrolled trial of abemaciclib, so in general, inferential statistical tests of treatment will not be performed. All tests of effects between subgroups of participants will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all CIs will be given at a 2-sided 95% level.

For all response-based evaluations of endpoint change from baseline, e.g., best overall response (BOR) by RECIST 1.1, PCWG3, or PSA value, the baseline value will be the last observation taken before treatment initiation that falls within the specified timeframe. Participants without an observation in this timeframe will be considered non-evaluable for the associated response.

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. 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.

The SAP will be finalized prior to First Patient First Visit 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 analyses of the most important endpoints including primary and key secondary endpoints.

9.4.2. Primary analysis

The primary analysis of the primary endpoint of ORR will be performed approximately 6 months after the last patient enters treatment and/or investigator-assessed best response assessments have been completed for all participants. All secondary endpoints will be evaluated at this time. Additional updated analyses of efficacy and safety may be conducted at later times if deemed appropriate by the sponsor.

At each analysis, the ORR will be evaluated against a null hypothesis of 5%. For the interim analysis of efficacy, all participants who have initiated treatment more than approximately 16 weeks prior to the data cut-off will be considered part of the at-risk population. For the primary analysis, responders will consist of those participants with a BOR of confirmed PR or confirmed CR, per RECIST 1.1 criteria, and do not have concurrent bone progression per PCWG3 at the time of the analysis. If 5 or more responders are observed from 40 treated participants, the study will be considered positive. This is equivalent to evaluating the binomial exact test with a null hypothesis that the ORR is 5% against an alternative of an ORR greater than 5% at a one-sided $\alpha = 0.05$.

Lilly or its designee will collect and store tumor assessment images, and an independent review of imaging scans may be performed by Lilly or its designee. Summaries of endpoints using independently reviewed BOR may be presented as sensitivity analyses, as described in the SAP.

9.4.3. Secondary endpoint(s)

Summaries of event rates, including radiologic ORR, and PSA-based response, will be defined as the proportion of all treated participants who achieve the specified response category. Participants with a non-evaluable or unknown response per specified criteria will be considered non-responders for the purpose of calculating the response rate.

Detailed censoring rules for time to event (TTE) endpoints are described in the SAP. For all TTE endpoints, median event times and rates at various time points, with 95% CI, will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for TTE will be described in the SAP.

9.4.4. Exploratory endpoint(s)

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9.4.5. Other Safety Analyses

All safety analyses will be made on the Safety Population, defined as all participants who receive at least 1 dose of study drug will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA®) Version [21.0 (or higher)] 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 (TEAEs) 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:

- TEAEs, including severity and possible relationship to study drug
- Treatment-emergent SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study intervention due to adverse events or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs

The number of participants with dose reductions, dose delays, or dose omissions will be summarized, as will the reasons for dose adjustments.

Reasons for death will be summarized separately for on-therapy and within 30 days of treatment discontinuation.

9.4.6. Other Analyses

9.4.6.1. Participant Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of participants enrolled in the study, and treated, as well as number and percentage of participants completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.4.6.2. Participant Characteristics

A summary of participant demographics, baseline participant and disease characteristics, historical diagnoses, preexisting conditions, and prior anti-cancer therapies will be reported using descriptive statistics.

Other participant characteristics will be summarized as deemed appropriate.

9.4.6.3. Treatment Compliance

Treatment compliance will be summarized for all treated participants.

Compliance information for study drug will be collected by counting any remaining tablets at each cycle. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \times 100$$

The actual cumulative dose taken will be determined based on counting the number of tablets returned at each visit and subtracting that number from the number of tablets dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions.

9.4.6.4. Extent of Exposure

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated participants.

9.4.6.5. Post-Abemaciclib Therapy

The numbers and percentages of participants receiving post-study-treatment discontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall and by line of therapy.

9.4.6.6. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on all participants who have received at least 1 dose of abemaciclib 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) 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.

9.4.6.7. Patient Reported Outcomes

Patient Reported Outcomes will be analyzed using descriptive statistics will be calculated for patient-reported data for each instrument. Further details will be described in the PRO SAP.

9.4.6.8. Biomarker Analysis

The percentage of cells expressing Ki-67 by immunohistochemistry (IHC) for each participant in the biomarker evaluable population will be summarized and listed. Additionally, Ki-67 expression values will be classified into a series of binary variables (e.g., <10%, <25%, etc.; see SAP for details), and the proportion of participants in each group will be reported with corresponding exact 95% CIs. Given a sample size of 40 patients, corresponding exact 95% CIs for a variety of observed prevalence rates are illustrated below.

Observed Prevalence Rate	95% Confidence Interval
0.05	(0.006, 0.169)
0.25	(0.127, 0.412)
0.5	(0.338, 0.662)
0.75	(0.588, 0.873)
0.95	(0.831, 0.994)

9.4.6.9. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

9.5. Interim Analyses

A futility analysis will be conducted approximately 2 months after the 15th participant has entered treatment. Trial enrollment will continue while awaiting the results of the futility analysis. The study team will consider the totality of safety, efficacy, and PK data. As guidance, futility should be declared and trial enrollment stopped if 0 patients have achieved an unconfirmed PR or CR per RECIST 1.1 AND fewer than 5 participants have achieved a BOR of SD per RECIST 1.1 at the time of the futility analysis.

One additional interim analysis of efficacy will be conducted approximately 2 months after all participants have entered treatment. Endpoints using RECIST 1.1 will be analyzed considering both confirmed and unconfirmed responses. The interim analysis will be conducted to evaluate the initial evidence of antitumor activity. The sponsor has no intent to stop the study based on the interim analysis of antitumor activity and all participants will continue follow-up for all study objectives until study close.

Additional interim analysis may be conducted as deemed appropriate by the sponsor.

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

9.6. Data Monitoring Committee (DMC)

Not applicable.

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 CIOMS International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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.
- 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 the study conduct for the participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
  - 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 his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act 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 re-consented 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 his/her 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 his/her 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 has 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.

10.1.5. Committees Structure

Not applicable.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., 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.
- Monitoring details describing strategy (e.g., 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 (e.g., 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, the 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 the 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 electronic data capture system (EDC) 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.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant into an instrument (for example, handheld smart phone or tablet, or by means of an interactive voice/web system). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture system 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. Prior to decommissioning, the investigator will receive 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 the results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse. Data from complaint forms submitted to sponsor will be encoded and stored in the global product complaint management system.

10.1.7. 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 the CRF or entered in the eCRF that 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.

10.1.8. Study and Site Start and Closure

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.

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:

- 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 of participants by the investigator
- Discontinuation of further study intervention development.

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.

10.1.9. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed as indicated in the table.

Local laboratory results are only required in the event that the central laboratory results are not available in time for inclusion/exclusion determination, study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is also obtained. If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (for example, hypertension, neutropenia, etc.) this should be reported in the CRF. Do not enter the test abnormality, enter the diagnosis or categorical term.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations and clinically significant findings should be reported in the CRF as an AE.

Enrollment and treatment decisions may be based on local laboratory results. A sample must still be sent to the central laboratory. Differences between these samples will not be considered a protocol deviation.

Hematology –[a, c]	
Leukocytes (WBC)	Basophils
Neutrophils[b]	Erythrocytes (RBC)
Lymphocytes	Hemoglobin (HGB)
Monocytes	Hematocrit (HCT)
Eosinophils	Platelets (PLT)
Mean corpuscular volume (MCV)	Mean corpuscular hemoglobin concentration (MCHC)

Clinical chemistry –[a, c] Serum concentrations of:	
Alanine aminotransferase (ALT)	Cystatin C
Albumin	Glucose (random)
Alkaline phosphatase	High-density lipoprotein (HDL)
Aspartate aminotransferase (AST)	Lactic acid dehydrogenase (LDH)
Bilirubin, direct	Low-density lipoprotein (LDL)
Bilirubin, total	Magnesium
Bicarbonate/CO_2	Phosphate
Blood urea nitrogen (BUN) or blood urea	Potassium
Calcium	Protein
Chloride	Sodium
Cholesterol	Triglycerides
Creatinine	Urate
Creatinine kinase (CK)	
Other Tests -[a, c]	
PSA	Testosterone

Abbreviations: CO_2 = carbon dioxide; CRF = case report form; PSA = prostate specific antigen; RBC = red blood cells; WBC = white blood cells.

[a] Central laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Enrollment and treatment decisions may be based on local laboratory results. A sample must still be sent to the central laboratory. Differences between these samples will not be considered a protocol deviation.

10.3. Appendix 3: 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 or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: 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 study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., 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 conditions 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. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of 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 which 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 (e.g., 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 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. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing 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 (e.g., 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

f. Other situations:

- Medical or scientific judgment should be exercised 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 usually 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. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the 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 the 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 v5.0 (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.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 his/her 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 his/her opinion of causality in light of follow-up information and send a 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.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

10.3.4. 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 paper SAE data collection tool (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 a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the SAE form.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by

telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- 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.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE (for study participants or their female partners if sexually active and if female partners are of childbearing age):
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Vasectomized partner *Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

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 obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also 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 including fetal status (presence or absence of anomalies) or indication for the procedure.

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

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly CRP/CRS.

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 8.2.2.1 for guidance on appropriate test selection.

- **For testing selected, analysis is required to be completed by the Lilly designated central laboratory except for Microbiology.**
- **Local testing may be performed in addition to central testing when required for immediate patient 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
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA [Quantitative])
Hepatitis A Virus (HAV) Testing:	Immunoglobulin G (IgG [Quantitative])
HAV Total Antibody	Immunoglobulin M (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[d]	Anti-actin antibody[b]
Hepatitis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA[d]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

Abbreviations: CRF = case report form; CRP = clinical research physician; CRS = clinical research scientist; DNA = deoxyribonucleic acid; Ig = immunoglobulin; INR = international normalized ratio; RNA = ribonucleic acid.

[a] This is not required if Anti-Actin Antibody is tested.

[b] This is not required if Anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed by Investigator-designated local laboratory ONLY; no Central Testing available. For some abnormal lab values, only the related diagnosis will be reported in the CRF.

[d] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.6. Appendix 6: Inducers and Strong Inhibitors of CYP3A

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

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St John's wort
Moderate Inducers of CYP3A
Bosentan
Lesinurad
Modafinil
Primidone
Telotristat ethyl
Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably <=7 days, if clinically indicated.

Abbreviations: CYP = cytochrome P450.

10.7. Appendix 7: 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 4-6 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 (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
Investigations					
Alanine aminotransferase (ALT) increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 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 a blood specimen.					
Aspartate aminotransferase (AST) increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 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.					

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

10.8. Appendix 8: Abbreviations

Term	Definition
ADT	androgen deprivation therapy
AE	adverse event
AI	Aromatase inhibitor
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BOR	best overall response
CDK	cyclin-dependent kinase
CDK 4&6	cyclin-dependent kinases 4 & 6
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
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
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRPC	castration-resistant prostate cancer
CRS	clinical research scientist
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome p450
DES	diethylstilbestrol

Term	Definition
DMC	data monitoring committee
DSMT	Developmental Safety Management Team
DSST	Developmental Safety Surveillance Team
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medical Agency
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.
EORTC QLC-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
ERB	Ethical review boards
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-GP5	GP5 item of the Functional Assessment of Cancer Therapy-General instrument, which asks participants to report the extent to which "(they are) bothered by side-effects of treatment"
FDA	Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone
GnRHa	gonadotropin-releasing hormone agonist or antagonist
HER2-	human epidermal growth factor receptor 2 negative
HR+	hormone receptor positive
IB	Investigator's Brochure
ICF	informed consent form

Term	Definition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IHC	immunohistochemistry
ILD	Interstitial lung disease
Informed consent	A process by which a participant voluntarily confirms his or her 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.
IRB	Institutional Review Boards
IV	intravenous
MATE	multidrug and toxin extrusion
MBC	metastatic breast cancer
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic hormone-sensitive prostate cancer
MRI	magnetic resonance imaging
NHA	Novel hormonal agent
nmCRPC	non-metastatic castration-resistant prostate cancer
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
PCa	prostate caner

Term	Definition
PCWG3	Prostate Cancer Clinical Trials Working Group 3
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
pRb	retinoblastoma protein
PRO	patient reported outcome
PRO-CTCAE	patient reported outcome- common terminology criteria for adverse events
PSA	prostate-specific antigen
PT	Preferred Term
QoL	Quality of Life
Rb	retinoblastoma gene
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
rPFS	radiographic progression free survival
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.
SD	stable disease
SoA	Schedule of Activities
SOC	System Organ Class
SSE	symptomatic skeletal event
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin

Term	Definition
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.
TTE	time to event
VTE	venous thromboembolic events

10.9. Appendix 9: Protocol Amendment History

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

Amendment a (24 September 2020)

This amendment is considered to be substantial 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:

This amendment incorporates changes in response to regulators' comments. In addition, this amendment includes changes made to clarify information for sites and minor grammatical, formatting, or spelling edits.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Clarification of Primary Endpoint	Administrative
1.3 Schedule of Activities	Added mobile healthcare service option to collect and process lab samples	Protocol flexibility
1.3.1 Sampling Schedule for Pharmacokinetics and Biomarkers	Added mobile healthcare service option to collect and process pharmacokinetic (PK) and biomarker plasma/blood samples	Protocol flexibility
1.3.1 Sampling Schedule for Pharmacokinetics and Biomarkers	Added blood microsampling to PK sampling schedule	Added blood microsampling instructions
2.3.1 Benefit Assessment	Updated new treatment options for metastatic castration-resistant prostate cancer (mCRPC) where approved	In response to regulators' comments
5.1 Inclusion Criteria	Clarification of Inclusion Criterion #1 to indicate participants' suitability for experimental therapy	In response to regulators' comments
5.2 Exclusion Criteria	Clarification on prior	Administrative

	investigational agent	
5.3 Lifestyle Considerations	Text was added to caution participants with known hypersensitivity or suspected intolerance to abemaciclib or any of its excipients	In response to regulators' comments
6.1 Study Intervention(s) Administered	Clarification on missed or vomited doses	Administrative
6.2 Preparation/Handling/Storage/Accountability	Clarification on study personnel responsibilities regarding study drug	Administrative
6.2.1 Selection and Timing of Doses	Clarification to indicate that additional study treatment may be dispensed for planned delays	Administrative
6.5 Concomitant Therapy	Clarification to refer to prescribing information for concomitant medications	In response to regulators' comments
7.2.1 Discontinuation of Inadvertently Enrolled Patients	Clarification on discontinuation of inadvertently enrolled patients	Administrative
7.3 Lost to Follow up	Clarification on designated study personnel	Administrative
8.1.1 Definitions of Efficacy Measures	Clarification was provided on definition of "Objective Response Rate" and for consistency, "Disease Control Rate	In response to regulators' comments
8.2.1 Clinical Safety Laboratory Assessments	Clarification on study personnel and responsibilities for designating local lab and	Administrative

	reporting of AEs.	
8.5 Pharmacokinetics	Updated PK collection instructions	Added blood microsampling instructions
8.8.1 Tissue Samples for Biomarker Research	Removed requirement of discussion with Lilly clinical research physician/scientist (CRP/CRS) for archival tissue	Administrative
8.10.2 Health Care Resource Utilization	Clarification on authorized study personnel	Administrative
9.2 Sample Size Determination	Clarification on "Objective Response"	Editorial
9.4.2 Primary Analysis	Clarification was provided on definition of "Objective Response Rate"	Administrative
10.1.1 Regulatory and Ethical Considerations	Clarification on investigator study oversight and responsibilities	Administrative
10.1.6 Data Quality Assurance	Updated instructions for data capture of eCOA	Administrative
10.2 Appendix 2: Clinical Laboratory tests	Removed "recorded" typo	Editorial

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