Protocol 13Y-MC-JPEF (d)

postMONARCH: A Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy of Abemaciclib Plus Fulvestrant to Placebo Plus Fulvestrant in Participants With HR+, HER2-, Advanced or Metastatic Breast Cancer Following Progression on a CDK4 & 6 Inhibitor and Endocrine Therapy

NCT05169567

Approval Date: 04-Oct-2023

Title Page

Protocol Title: postMONARCH: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy of Abemaciclib plus Fulvestrant to Placebo plus Fulvestrant in Participants with HR+, HER2-, Advanced or Metastatic Breast Cancer Following Progression on a CDK4 & 6 Inhibitor and Endocrine Therapy

Protocol Number: I3Y-MC-JPEF

Amendment Number: d

Compound: Abemaciclib (LY2835219)

Brief Title: Abemaciclib plus Fulvestrant compared to Placebo plus Fulvestrant in HR+, HER2-, Advanced or Metastatic Breast Cancer previously treated with a CDK4/6 Inhibitor and Endocrine Therapy

Study Phase: 3

Acronym: postMONARCH

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Numbers:

IND: 106100

EudraCT: 2021-002301-10

EU Trial Number: 2023-506771-10-00

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

Document ID: VV-CLIN-050468

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	*17-Feb-2022*
Amendment b	*09-Dec-2021*
Amendment a	*02-Sep-2021*
Original Protocol	*13-Aug-2021*

Amendment (d)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to align with EU Clinical Trial Regulation (EU-CTR) requirements.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added EU Trial Number Study Population e z ((– (R ” ’ .≧(z (≧.–.’ .≧(• (Vn (T♂ ’≤z◁(m ’z◁(k .:“ ◁z ’ (’ (Study Intervention Ethical Considerations of Benefit/Risk	For EU CTR compliance
1.1. Synopsis 4.1. Overall Design	Added definition of visceral metastases: ’ ≤. .z◁(’ ≤○≥. .(○ “6(♂ ..6(• z’ 6(○.. z◁6(z ≥(…’ .z◁(’ ○ .● … (	For clarification
1.3. Schedule of Activities (SoA)	Updated the age of women from <60 years (LDD(.z (’ (W a (… for consistency with Inclusion Criteria and Appendix 4.	For clarification
1.3. Schedule of Activities 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 8.3.1 Timing and Mechanism for Collecting Events 10.3.1 Definition of AE	Added statement about the reporting of AEs and SAEs, including death, caused by disease progression or otherwise due to study disease.	For clarification
5.1. Inclusion Criteria	Updated the contraception language for WOCBP	To comply with updated guidance

Section # and Name	Description of Change	Brief Rationale
6. Study Intervention(s) and Concomitant Therapy	Updated the definition of study intervention	For EU CTR compliance
6.1. Study Intervention(s) Administered	Added last row for R ” ’ .≧(z (defined by EU Clinical Trial k .:‘ ◌z ’ R≥≥.≧(z(z z“ z ”((i z≤×z“’ “(z ≥(◌z• . ◌̈ “	
9.3.1. General Considerations	Added a paragraph on handling of missing, unused, and spurious data	
10.1.1. Regulatory and Ethical Considerations	Added a bullet point regarding reporting of significant issues related to z ’≤’ z (z¬… 6(”“” 6(z ≥(≥z z(integrity	
10.1.4. Data Protection	Updated the required language	
10.1.6. Dissemination of Clinical Study Data	Updated the required language in k …	
10.3.1. Definition of AE	R≥≥.≧(z(• ◌̧.(’ (V … (f ….…’ “(”.(. RV(U.¬’ ’ ’	
10.3.6. Regulatory Reporting Requirements	n ≥z .≧(”.(…. ’ .≧(◌z “ z“.(: (l RV(k .:‘ ◌z (k … ’ “	
10.4.1 Definitions	Women not of child bearing potential row: updated the bullet for congenital anomaly added acceptable surgical sterilization methods Post-menopausal state row: changed FSH value from >40 to C; mIU/mL	To comply with updated guidance
10.4.2. Contraception Guidance	Updated the language for WOCBP Updated the contraception language for WOCBP Added examples of highly effective contraception Added a note that male and female condoms should not be used in combination for effective contraception Deleted immunocontraceptives from ineffective forms of contraception	
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments	Deleted segmented from neutrophils	

Section # and Name	Description of Change	Brief Rationale
10.9. Appendix 9. Abbreviations and Definitions	Added abbreviations and definitions	For EU CTR compliance
10.10. Appendix 10: Protocol Amendment History	Inserted date, rationale, and summary of changes from amendment (c).	To update document history
Throughout the protocol	Minor formatting and editorial changes	For correction. Minor, therefore, not detailed

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: postMONARCH: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy of Abemaciclib plus Fulvestrant to Placebo plus Fulvestrant in Participants with HR+, HER2-, Advanced or Metastatic Breast Cancer Following Progression on a CDK4 & 6 Inhibitor and Endocrine Therapy

Brief Title: Abemaciclib plus Fulvestrant compared to Placebo plus Fulvestrant in HR+, HER2-, Advanced or Metastatic Breast Cancer previously treated with a CDK4/6 Inhibitor and Endocrine Therapy

Regulatory Agency Identifier Numbers:

IND: 106100

EudraCT: 2021-002301-10

EU Trial Number: 2023-506771-10-00

Rationale:

The incorporation of CDK4 & 6 inhibitors with endocrine therapy (ET) into first-line treatment of locally advanced or metastatic hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer has dramatically improved outcomes (Finn et al. 2016; Tripathy et al. 2018; Johnston et al. 2019). However, these therapies are not curative, and nearly all MBC patients will experience disease progression. More recently, abemaciclib has shown significant improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in the adjuvant setting (Johnston et al. 2020). As the use of CDK4 & 6 inhibitors increases in earlier lines of therapy, the question of how to best treat patients following disease progression or relapse after CDK4 & 6-based therapy will become increasingly important to inform future practice.

Following disease progression on a CDK4 & 6 inhibitor plus ET, there are a number of treatment options. However, most of these treatment options were tested before CDK4 & 6 inhibitors were available, with the exception of alpelisib in the BYLieve study (Rugo et al. 2021). Therefore, outcomes following treatment with a CDK4 & 6 inhibitor-containing therapy are not well understood, and there are no prospective Phase 3 studies to guide therapy for this population.

Following CDK4 & 6 inhibitor-containing therapy, resistance mechanisms are multifactorial and could include resistance directed to the ET and/or CDK4 & 6 inhibitor component of the regimen (Alvarez-Fernandez and Malumbres 2020). Importantly, tumors that have developed class-specific ET resistance (for example, *ESR1* mutations in the setting of aromatase inhibitors) may have continued dependence on CDK4 & 6 pathway inhibition. Given the safety and tolerability of CDK4 & 6 inhibitors in combination with ET, there is growing interest in testing the continuation of CDK4 & 6 inhibition beyond progression while switching the ET backbone. Benefit from continuation of therapy beyond progression has been established in other disease states, such as in HER2+ MBC where HER2-directed therapy is continued while a new ET or cytotoxic chemotherapy regimen is initiated (von Minckwitz et al. 2011; Baselga et al. 2012b).

The ability to maintain disease control through multiple lines of endocrine-based therapies suggests persistent dependence on endocrine signaling after disease progression (Weatherman et al. 1999; Baselga et al. 2012a). Switching to an ET partner with a different mechanism provides continued endocrine signaling inhibition that can induce response or control disease progression, thus delaying the need for chemotherapy. Fulvestrant, a selective ER degrader (SERD), is one such option and is approved for use in the second-line setting.

There is an unmet need to understand and improve outcomes in this setting through the evaluation of novel strategies in Phase 3 randomized trials. postMONARCH is a randomized, Phase-3 study of fulvestrant with or without abemaciclib in participants with HR+, HER2- advanced or metastatic breast cancer with disease progression on/after either adjuvant or first-line treatment with a CDK4 & 6 inhibitor plus ET.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the efficacy of fulvestrant with or without abemaciclib	PFS as determined by investigator assessment using RECIST 1.1
Secondary	
To further compare the efficacy of fulvestrant with or without abemaciclib	OS PFS by BICR ORR CBR DCR DoR
To further characterize the safety profile of abemaciclib in combination with fulvestrant	Safety including but not limited to TEAEs, SAEs, deaths, and clinical laboratory abnormalities
To compare PRO measures of fulvestrant with or without abemaciclib	Time to worsening in worst pain via the mBPI-SF worst pain item Time to deterioration in physical function via the EORTC IL-19
To characterize the pharmacokinetics (PK) of abemaciclib in combination with fulvestrant	Concentrations of abemaciclib

Abbreviations: BICR = blinded independent central review; CBR = clinical benefit rate; DCR = disease control rate; DoR = duration of response; EORTC IL-19 = European Organisation for Research and Treatment of Cancer Item Library 19; mBPI-SF = modified Brief Pain Inventory-short form; ORR = objective response rate; OS = overall survival; PRO = patient-reported outcome; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design

postMONARCH is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study in participants with HR+, HER2- advanced or metastatic breast cancer. This study will enroll adults who experienced disease progression on a CDK4 & 6 inhibitor and an AI in the first-line setting or relapse on/after a CDK4 & 6 inhibitor with ET in the adjuvant setting. The intervention arms include:

- Arm A: abemaciclib and fulvestrant (Investigational)
- Arm B: placebo and fulvestrant (Control)

Randomization will be 1:1 and stratified by the following factors:

- geography: CCI
- presence of visceral metastases: yes or no (visceral includes lung, liver, brain, pleural, and peritoneal involvement), and
- duration on prior adjuvant/metastatic CDK4 & 6 inhibitor-based regimen (2 levels):

CCI

The primary endpoint of PFS will be based upon investigator assessment.

Duration of Treatment:

Participants will be treated until disease progression or other discontinuation criteria are met.

Study Population

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

- ≥18 years of age (or of an acceptable age according to local regulations, whichever is older) at the time of signing the informed consent
- have a diagnosis of HR+, HER2- breast cancer
- have either advanced disease not amenable to curative surgical treatment or metastatic disease
- have radiologic evidence of disease progression or recurrence either
    - on treatment with a CDK4 & 6 inhibitor plus AI as initial therapy for advanced disease, or
    - on/after treatment with a CDK4 & 6 inhibitor plus ET administered as adjuvant therapy for early-stage breast cancer, and
- have either measurable disease or non-measurable but evaluable disease as defined by RECIST Version 1.1.

Number of Participants:

Approximately 350 participants will be randomly assigned to study intervention.

Study Intervention:

	Arm A		Arm B	
Treatment	**Abemaciclib**	**Fulvestrant**	**Placebo**	**Fulvestrant**
Dose	150 mg	500 mg	Matched to abemaciclib	500 mg
Route	PO	IM	PO	IM
Schedule	BID on Days 1-28 of each cycle	C1D1 and C1D15, then on Day 1 of Cycle 2 and subsequent cycles	BID on Days 1-28 of each cycle	C1D1 and C1D15, then on Day 1 of Cycle 2 and subsequent cycles
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization	Authorized and not used according to EU authorization	Not authorized in EU	Authorized and not used according to EU authorization

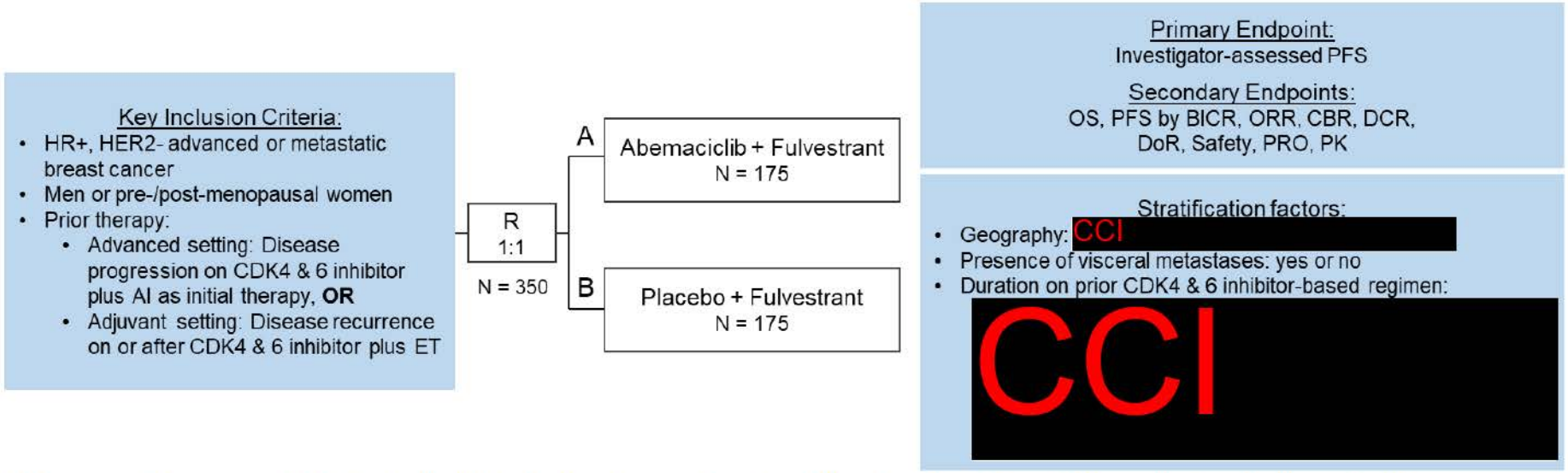
Abbreviations: BID = twice daily; C = cycle; D = day; IM = intramuscular; mg = milligrams; PO = orally.

Ethical Considerations of Benefit/Risk

The potential risks of the abemaciclib plus fulvestrant combination are justified in consideration of the measures to minimize these risks and the anticipated benefit of improved disease control, as measured by improved PFS in participants with HR+, HER2- MBC, an incurable disease with a poor prognosis and limited non-cytotoxic therapeutic options.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: AI = aromatase inhibitor; BICR = blinded independent central review; CBR = clinical benefit rate; CDK = cyclin-dependent kinase; DCR = disease control rate; DoR = duration of response; ET = endocrine therapy; HER = human epidermal growth factor receptor; HR = hormone receptor; N = number of participants; ORR= objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics: PRO = patient-reported outcomes; R = randomization.

1.3. Schedule of Activities (SoA)

This section includes the following SoAs:

Screening, Treatment, and Post-Discontinuation Follow-Up SoA for all participants
Continued-Access SoA for participants on abemaciclib

Overview
The windows for the SoA and administration of first dose are based on calendar days.

Study Period I Screening & Baseline
The screening period allows up to 28 days for confirmation of eligibility and completion of baseline assessments.

Study Period II Treatment
During the on-study treatment period, participants will return to clinic every 2 weeks (14 ± 3 days) for the first 2 cycles, and then monthly (28 ± 7 days) starting with Cycle 3 until start of short-term follow-up. The duration of this study period is not predefined as patients will remain on treatment until disease progression or discontinuation for any reason.

Tumor Response
Tumor response per RECIST 1.1 should be assessed approximately every 8 weeks for the first 12 months (relative to Cycle 1 Day 1), and thereafter approximately every 12 weeks until the participant has objective disease progression, death, or study completion (following evaluation of final OS data).

Study Period III Short- and Long-Term Follow-Up
Participants discontinuing study intervention will return for an in-clinic short-term follow-up visit (Visit 801). The short-term follow-up visit will take place 30 days (±7 days) after the decision is made to discontinue all study treatment.

After the short-term follow-up visit, all participants will enter the long-term follow-up period (Visit 802-8XX). Long-term follow-up begins the day after the short-term follow-up visit is completed and continues until z ’≤’ z (≥. z ”, withdrawal from study, or study completion. Long-term follow-up visits should occur approximately every 2-3 months (Q60-90D) during long-term follow-up. The duration of this study period is not predefined as participants will remain in long-term follow-up until death, withdrawal from study, or study completion.

Screening, Treatment, and Post-Discontinuation Follow-Up SoA for All Participants

	Study Period	**Study Period I Screening[a]**	**Study Period II Treatment Period (Cycle = 28 Days)**			**Study Period III Post-Discontinuation Follow-Up Period**		
	Cycle/Visit	**Baseline**	**Cycles 1-2**		**Cycle 3-n**	**Short-Term[b] V801**	**Long-Term[c] V802-V8XX**	**Notes**
	Relative Day within a Cycle	**i s**	**D1**	**D15**	**D1**	**30 Days**	**(Q60-90D)**	For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		**-3**	**±3**	**±7**	**±7**		-3 days for C1D1 ± 3 days for C1D15, C2D1, and C2D15 ± 7 days for C3D1-n
Procedure Category	**Procedure**							
Study Entry/Enrollment	Informed consent	X						ICF must be signed before any protocol-specific procedures are performed
	Inclusion and exclusion criteria	X	See note					Must be confirmed prior to randomization
	Demographics	X						
Medical History	Preexisting conditions and medical history, including relevant surgical history	X						
	Prior treatments for breast cancer	X						Record cancer surgery, radiation, prior anticancer therapies
	Substance use (alcohol, tobacco use)	X						
Concomitant Medications		X	X	X	X	X		Record all premedication, supportive care, and concomitant medication
Adverse Event Collection/CTCAE Grading		X	X	X	X	X	X	CTCAE Version 5.0 AEs, including SAEs, are collected at every clinic visit, throughout the on-study intervention period and short-term follow-up, regardless of relationship to study intervention AEs and SAEs, including death, caused by disease progression or otherwise due to study disease should not be reported unless the

	Study Period	**Study Period I Screening[a]**	**Study Period II Treatment Period (Cycle = 28 Days)**			**Study Period III Post-Discontinuation Follow-Up Period**		
	Cycle/Visit	**Baseline**	**Cycles 1-2**		**Cycle 3-n**	**Short-Term[b] V801**	**Long-Term[c] V802-V8XX**	**Notes**
	Relative Day within a Cycle	**i s**	**D1**	**D15**	**D1**	**30 Days**	**(Q60-90D)**	For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		**-3**	**±3**	**±7**	**±7**		-3 days for C1D1 ± 3 days for C1D15, C2D1, and C2D15 ± 7 days for C3D1-n
Procedure Category	**Procedure**							
								investigator deems them to be possibly related to study treatment. For long-term follow-up: only SAEs that are related to study drugs or protocol procedures will be collected
Survival Information						X	X	
Post-Discontinuation Treatment						X	X	
Physical Evaluation	Height	X						
	Weight	X	X	X	X	X		
	Vital signs	X	X	X	X	X		Temperature, blood pressure, pulse rate, and respiration rate If collected within 7 days of D1, they do not need to be repeated at D1
	Complete physical examination	X	X					Excludes pelvic and rectal exams C1D1 only If collected within 7 days of D1, does not need to be repeated
	Symptom-directed physical examination		See note		X	X	X	C2D1 and Day 1 of each cycle after C2
	ECOG PS status evaluation	X	X		X	X		

	Study Period	Study Period I — Screening[a]	Study Period II — Treatment Period (Cycle = 28 Days)			Study Period III — Post-Discontinuation Follow-Up Period		
	Cycle/Visit	Baseline	Cycles 1-2		Cycle 3-n	Short-Term[b] V801	Long-Term[c] V802-V8XX	Notes
	Relative Day within a Cycle	≤28	D1	D15	D1	30 Days	(Q60-90D)	• For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		-3	±3	±7	±7		• -3 days for C1D1 • ± 3 days for C1D15, C2D1, and C2D15 • ± 7 days for C3D1-n
Procedure Category	Procedure							
Clinical Tumor Assessment Refer to Section 8.1	CCI							
Tumor Assessment Refer to Section 8.1								

	Study Period	Study Period I — Screening[a]	Study Period II — Treatment Period (Cycle = 28 Days)			Study Period III — Post-Discontinuation Follow-Up Period		
	Cycle/Visit	Baseline	Cycles 1-2		Cycle 3-n	Short-Term[b] V801	Long-Term[c] V802-V8XX	Notes
	Relative Day within a Cycle	≤28	D1	D15	D1	30 Days	(Q60-90D)	• For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		-3	±3	±7	±7		• -3 days for C1D1 • ± 3 days for C1D15, C2D1, and C2D15 • ± 7 days for C3D1-n
Procedure Category	Procedure							
Tumor Assessment Refer to Section 8.1	CCI							
Brain Imaging Refer to Section 8.1								

	Study Period	Study Period I — Screening[a]	Study Period II — Treatment Period (Cycle = 28 Days)			Study Period III — Post-Discontinuation Follow-Up Period		
	Cycle/Visit	Baseline	Cycles 1-2		Cycle 3-n	Short-Term[b] V801	Long-Term[c] V802-V8XX	Notes
	Relative Day within a Cycle	≤28	D1	D15	D1	30 Days	(Q60-90D)	• For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		-3	±3	±7	±7		• -3 days for C1D1 • ± 3 days for C1D15, C2D1, and C2D15 • ± 7 days for C3D1-n
Procedure Category	Procedure							
Tumor Assessment Refer to Section 8.1	CCI							
Patient Dosing Diary (Paper)			See notes					• Dispense diary on D1 of C1 and C2 • Participants record date and times of every dose of blinded study drug taken from C1D1 through C3D1 • Collect and review diary from prior cycle on D1 of C2 and C3 • See Section 1.3.2 for use with site PK dosing data entry
Lab/diagnostic tests	12-lead ECG (Single, local)	X						

	Study Period	Study Period I — Screening[a]	Study Period II — Treatment Period (Cycle = 28 Days)			Study Period III — Post-Discontinuation Follow-Up Period		
	Cycle/Visit	Baseline	Cycles 1-2		Cycle 3-n	Short-Term[b] V801	Long-Term[c] V802-V8XX	Notes
	Relative Day within a Cycle	≤28	D1	D15	D1	30 Days	(Q60-90D)	• For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		-3	±3	±7	±7		• -3 days for C1D1 • ± 3 days for C1D15, C2D1, and C2D15 • ± 7 days for C3D1-n
Procedure Category	Procedure							
Lab/Diagnostic Tests See Section 10.2, Appendix 2	[redacted]							
Health Outcomes	PROs and HCRU		See Section 1.3.1					

	Study Period	Study Period I — Screening[a]	Study Period II — Treatment Period (Cycle = 28 Days)			Study Period III — Post-Discontinuation Follow-Up Period		
	Cycle/Visit	Baseline	Cycles 1-2		Cycle 3-n	Short-Term[b] V801	Long-Term[c] V802-V8XX	Notes
	Relative Day within a Cycle	≤28	D1	D15	D1	30 Days	(Q60-90D)	• For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		-3	±3	±7	±7		• -3 days for C1D1 • ± 3 days for C1D15, C2D1, and C2D15 • ± 7 days for C3D1-n
Procedure Category	Procedure							
Biomarker, Genetic, Pharmacokinetic, Tissue Collection	CCI							

	Study Period	Study Period I Screening[a]	Study Period II Treatment Period (Cycle = 28 Days)			Study Period III Post-Discontinuation Follow-Up Period		
	Cycle/Visit	Baseline	Cycles 1-2		Cycle 3-n	Short-Term[b] V801	Long-Term[c] V802-V8XX	Notes
	Relative Day within a Cycle	i s	D1	D15	D1	30 Days	(Q60-90D)	For V802-V8XX, phone visits are acceptable
	Visit Interval Tolerance (Days)		-3	±3	±7	±7		-3 days for C1D1 ± 3 days for C1D15, C2D1, and C2D15 ± 7 days for C3D1-n
Procedure Category	Procedure							
	Dosing							
Study Drug Dosing See Section 6.1.2	Dispense blinded study drug		X		X			
	Blinded study drug dosing		See note					Orally BID on Days 1-28 of each cycle
	Fulvestrant dosing		See notes					IM on C1D1 and C1D15, then on Day 1 of Cycle 2 and beyond If participant misses the specified window around D1, administration should occur at earliest opportunity and not wait until following cycle to resume
	Observe participant administer oral study drug		See notes					During PK cycles only Cycles 1-3 Observation is to ensure proper timing of PK sampling See Section 1.3.2
	Participant returns study drugs		See note					Return at Day 1 of C2 and beyond and V801 if applicable to assess compliance

Abbreviations: AE = adverse event; BID = twice daily; C = Cycle; CRP/CRS = clinical research physician or clinical research scientist; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FSH = follicle-stimulating hormone; HCRU = health care resource utilization; ICF = informed consent form; IM = intramuscular; MRI = magnetic resonance imaging; PK = pharmacokinetics; PRO = patient-reported outcomes; Q = every; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SOC = standard of care; V = visit; WOCBP = women of child-bearing potential.

a Screening procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.

b Short-term follow-up begins the day after the participant and the investigator agree that the participant will no longer continue study treatment and lasts approximately 30 days; the associated study procedures are performed once at the end of this period.

c Long-term follow-up begins the day after short-term follow-up is completed and continues until the participant's death or overall study termination; the associated study procedures are performed every 60-90 days for the duration of this period.

Continued-Access SoA (See also Section 6.6)

Visit[a]	Study Intervention	Continued-Access 30-Day Follow-Up	Instructions
	501-5XX	**901**	
Duration (days)	**28**	**30±5**	
AE collection	X	X	Per CTCAE v5.0 Collect all AEs and SAEs regardless of causality during the continued-access and follow-up periods
Administer study intervention	X		See Section 6.1 for study intervention administration details and guidelines

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

[a] The continued-access period begins after study completion and ends at the end of trial.

1.3.1. Schedule of Assessments for Patient-Reported Outcomes and HCRU

		Completed at Home during All Cycles until Last Visit (SFU)	Short-Term Follow-Up (30 days)[a]	Instructions
Instrument	CCI	CCI	CCI	• Participants complete using ePRO device
Worst Pain Single Item	CCI	CCI	CCI	• "Worst Pain Single Item" is CCI as a single item and is also one of the 11 items in the mBPI-SF scale • CCI
mBPI-SF Scale	CCI	CCI	CCI	• CCI
PRO-CTCAE-Diarrhea	CCI	CCI	CCI	• CCI
EORTC QLQ-C30[b]	CCI	CCI	CCI	CCI
EORTC IL-19[b]	CCI	CCI	CCI	CCI
EQ-5D-5L	CCI	CCI	CCI	• CCI
HCRU	CCI	CCI	CCI	• CCI

Abbreviations: C = cycle; CRF = case report form; D = day; EORTC IL-19 = European Organization for Research and Treatment of Cancer Item Library 19; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30; ePRO = electronic patient-reported outcomes; EQ-5D-5L = 5-level-EuroQol; HCRU = health care resource utilization; mBPI-SF = modified Brief Pain Inventory-short form; PROs = patient-reported outcomes; PRO-CTCAE = Patient-Reported Outcomes – Common Terminology Criteria for Adverse Events; SFU = short-term follow-up.

[a] Short-term follow-up begins the day after the participant and the investigator agree that the participant will no longer continue study treatment and lasts approximately 30 days; the associated study procedures are performed once at the end of this period.

CCI

1.3.2. PK Sampling Schedule

Pharmacokinetics (PK) samples will be collected from all participants as specified below. Samples will be analyzed for concentrations of abemaciclib and its active metabolites, M2 and M20.

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

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

the morning of the planned PK collection and
the morning and evening doses taken the day before the planned PK collection (Cycle 2 and beyond).

Pharmacokinetic Sampling Schedule

Sampling Day	Sample Number	Microsample PK	Plasma PK
Cycle 1 Day 1	1	Any time at least 1 h after the first blinded study drug dose[a]	Within ±10 minutes of microsample
Cycle 2 Day 1	2	Predose[b,c]	None
	3	Any time at least 4 h after the first daily blinded study drug dose[a,c,d]	None
Cycle 3 Day 1	4	Predose[b]	Within ±10 minutes of microsample

Abbreviations: h = hours; PK = pharmacokinetics.

a The PK sample should be collected after the morning dose of blinded study drug.

b Participants should refrain from taking blinded study drug until arrival at the clinic. Blinded study drug administration may resume following the PK sample draw.

c The sample may be collected by the participant or caregiver.

d A minimum of 4 hours should separate PK samples on Cycle 2 Day 1.

2. Introduction

This is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study for participants with HR+, HER2- MBC with disease progression on a CDK4 & 6 inhibitor and ET. The study will evaluate the benefits of continuing CDK4 & 6 inhibition while switching the class of ET partner to a SERD (fulvestrant). Specifically, the study will enroll adults with disease progression on a CDK4 & 6 inhibitor and an AI in the first-line metastatic setting or on/after a CDK4 & 6 inhibitor in combination with ET in the adjuvant setting.

2.1. Study Rationale

The incorporation of CDK4 & 6 inhibitors with ET into first-line treatment of HR+, HER2- MBC has dramatically improved outcomes (Finn et al. 2016; Tripathy et al. 2018; Johnston et al. 2019). However, these therapies are not curative, and nearly all patients will experience disease progression. Additionally, CDK4 & 6 inhibitors are being tested in the adjuvant setting in patients with HR+, HER2-, high-risk, early breast cancer. The monarchE trial demonstrated significant and clinically meaningful improvement in IDFS and DRFS with the addition of abemaciclib to adjuvant ET (Johnston et al. 2020).

Numerous options exist for the treatment of MBC following disease progression on a CDK4 & 6 inhibitor; however, most of these therapies were tested in clinical trials before CDK4 & 6 inhibitors became standard of care as first or later lines of MBC treatment. Therefore, outcomes for many of these therapies in patients who have received a prior CDK4 & 6 inhibitor are not well understood.

Notably, there are no results from prospective Phase 3 studies to guide therapy for patients who develop disease progression during treatment with a CDK4 & 6 inhibitor and, although clinical guidelines offer various treatment options, there is no universally accepted standard of care for these patients. Thus, there is an unmet need to understand and improve outcomes through the evaluation of novel strategies in Phase 3 randomized trials.

Underlying reasons for disease progression during treatment with a CDK4 & 6 inhibitor and ET are multifactorial but include primary or secondary resistance to the ET component of the regimen, which is commonly an aromatase inhibitor or tamoxifen. Tumors that develop endocrine resistance (e.g., through an *ESR1* mutation, a common mechanism of acquired ET resistance) may have continued dependence on inhibition of the CDK4 & 6 pathway. Given the safety and tolerability of CDK4 & 6 inhibitors in combination with ET, there is growing interest in testing the continuation of CDK4 & 6 inhibition while switching the ET backbone to treat disease progression. Benefit from continuation of therapy beyond progression has been established in other disease states, such as in HER2+ MBC where HER2-directed therapy is continued while a new ET or cytotoxic chemotherapy regimen is initiated (von Minckwitz et al. 2011; Baselga et al. 2012b).

The ability to maintain disease control through multiple lines of endocrine-based therapies suggests persistent dependence on endocrine signaling after disease progression (Weatherman et al. 1999; Baselga et al. 2012a). Switching to an ET partner with a different mechanism of action provides continued endocrine signaling inhibition that can induce response or control disease

progression, thus delaying the need for chemotherapy. Fulvestrant is a SERD approved for use in the second-line setting and has proven efficacy.

2.2. Background

Globally, in 2020, breast cancer was the most common cancer diagnosed in females and the most common cause of cancer-related death among females (Sung et al. 2021). Most cases of MBC occur after locoregional and systemic treatments that were administered with curative intent. While CDK4 & 6 inhibition in combination with ET for initial treatment of HR+, HER2- MBC is effective and well tolerated, most patients ultimately develop progressive disease (Dickler et al. 2017; Gul et al. 2018; NCCN 2021).

It is unclear if disease progression is the result of resistance to the ET, the CDK4 & 6 inhibitor, or both (McCartney et al. 2019). The ability to maintain disease control through multiple lines of endocrine-based therapies that have differing mechanisms of action suggests that some breast cancers retain a persistent dependence on endocrine signaling after disease progression (Weatherman et al. 1999; Baselga et al. 2012a). Additionally, tumors that have developed resistance to first-line ET and CDK4 & 6 inhibitor may have continued benefit from CDK4 & 6 pathway inhibition when combined with an ET with a different mechanism of action.

This trial will test abemaciclib plus fulvestrant compared to single-agent fulvestrant in participants with disease progression on a CDK4 & 6 inhibitor and ET. Fulvestrant is a SERD that is approved for use in the second-line setting for the treatment of HR+ MBC. Single-agent fulvestrant was selected as the control arm as the drug is commonly used as second-line therapy in patients with disease progression during first-line therapy of an AI in combination with a CDK4 & 6 inhibitor. Abemaciclib is a CDK4 & 6 inhibitor with proven benefit in PFS and OS in patients with MBC (Dickler et al. 2017; Spring et al. 2019; Sledge et al. 2020). Importantly, abemaciclib has demonstrated improved efficacy and OS when combined with fulvestrant compared to fulvestrant alone as second- or third-line therapy for treatment of HR+, HER2- MBC.

In addition to the unmet clinical need, the rationale is supported by real-world, retrospective studies that have documented the off-label use of CDK4 & 6 inhibitor drugs in this population. These studies provide preliminary data suggesting clinical benefit when abemaciclib is administered following disease progression during treatment with a CDK4 & 6 inhibitor (Mariotti et al. 2020, Martin et al. 2021; Wander et al. 2021).

2.2.1. Treatment Options for HR+, HER2- Breast Cancer after Disease Progression or Recurrence on a CDK4 & 6 Inhibitor-Based Regimen

Importantly, there are no Phase 3 studies in this patient population to guide therapy. Given this lack of prospective evidence and an absence of standard care for relapsed MBC in the post-CDK4 & 6 inhibitor setting, the 2020 ESMO and 2021 NCCN clinical guidelines support the use of various options including

ET alone: aromatase inhibitors (AIs), selective ER modulators (SERMs), or SERDs
ET in combination with PI3K pathway blockade, usually with everolimus or alpelisib (if an actionable *PIK3CA* mutation is detected)
cytotoxic chemotherapy, and

clinical trial participation.

Little direct data exist to define the best therapy for HR+ MBC after a CDK4 & 6 inhibitor. Moreover, while in some locations, everolimus and alpelisib in combination with second-line ET are approved (alpelisib specifically in patients with *PIK3CA* mutations), these data were generated exclusively in CDK4 & 6 inhibitor naive patients (Baselga et al. 2012a; André et al. 2019), with the exception of alpelisib in the BYLieve study (Rugo et al. 2021). Thus, the efficacy of these agents post-CDK4 & 6 inhibitor treatment is unknown, and there is an unmet need to understand and improve outcomes through the evaluation of novel strategies in Phase 3 randomized trials. Additionally, everolimus and alpelisib have substantial toxicities and not all patients are appropriate or willing to receive them. These factors collectively support the selected control arm of second-line fulvestrant monotherapy.

2.2.2. CDK4 & 6 Inhibition in HR+, HER2- Breast Cancer

The CDK4 & 6 retinoblastoma (Rb) axis plays a critical role in HR+, HER2- breast cancer. Mechanistically, the CDK4/6-cyclin D1 complex phosphorylates the Rb tumor suppressor protein leading to a loss of repression of E2F transcription factors, resulting in cell-cycle progression from G1 to S phase, and cancer proliferation. From a therapeutic standpoint, the goal of inhibiting CDK4 & 6 is to prevent cell-cycle progression, thus arresting tumor growth.

Abemaciclib (Verzenio [LY2835219]) is an CDK4 & 6 inhibitor that is most active against cyclin D1/CDK4 in enzymatic assays, thereby preventing Rb phosphorylation, blocking progression from G1 into S phase of the cell cycle, and leading to suppression of tumor growth. Abemaciclib is approved for HR+, HER2- MBC based on improvements in PFS when added to anti-estrogen therapy (Spring et al. 2019). Abemaciclib is also approved as single-agent therapy for the treatment of HR+, HER2- MBC (Dickler et al. 2017). OS benefit has been confirmed for abemaciclib in combination with fulvestrant (Sledge et al. 2020) in ET-resistant MBC.

Recently, results from 3 Phase 3 adjuvant studies of CDK4 & 6 inhibitors have been published, with abemaciclib being the only CDK4 & 6 inhibitor to show significant improvement in invasive disease-free survival (IDFS) and distant relapse free survival (DRFS) in the adjuvant setting in the monarchE study (Johnston et al. 2020; Loibl et al. 2021; Mayer et al. 2021).

In HR+ breast cancer cell lines, sustained inhibition by abemaciclib prevents rebound of Rb phosphorylation and cell-cycle re-entry, resulting in senescence and apoptosis. In xenograft models, abemaciclib dosed daily without interruption at clinically relevant concentrations as a single agent or in combination with antiestrogens induced tumor response captured as a measurable reduction in tumor size. Abemaciclib is the only CDK4 & 6 inhibitor approved for continuous administration.

2.2.3. The Role of Endocrine Treatment in HR+, HER2- Breast Cancer

Over two-thirds of breast cancers express the estrogen receptor (ER), a key driver of breast cancer initiation and progression. Multiple means of ER signaling inhibition to exploit tumor dependency on estrogens are available. These include selective estrogen modulators (SERMs; tamoxifen), aromatase inhibitors (AIs; letrozole, anastrozole, and exemestane), and selective ER degraders (SERDs; fulvestrant). Patients with estrogen ER+ MBC often respond to ET alone or in combination with targeted agents, reducing tumor burden and symptoms with generally less

toxicity than chemotherapy, and thus form the backbone of initial MBC therapy (Cardoso et al. 2020; NCCN 2021).

While first-line ET is typically highly effective, especially in combination with CDK4 & 6 inhibitors (Finn et al. 2016; Hortobagyi et al. 2016; Goetz et al. 2017), nearly all patients experience disease progression (Lei et al. 2019). Importantly, dependence on ER signaling can persist despite progression, as demonstrated by the ability to maintain disease control in some patients through multiple lines of endocrine-based therapies (Weatherman et al. 1999; Baselga et al. 2012a; Turner et al. 2015; Finn et al. 2016; André et al. 2019).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of abemaciclib may be found in the b … ”“z (S ≤” .6(i z≤×z“.(. Insert, or Summary of Product Characteristics.

2.3.1. Risk Assessment

Study Intervention

This study aims to compare the efficacy and safety of abemaciclib plus fulvestrant (Arm A) versus placebo plus fulvestrant (Arm B).

1. Arm A: abemaciclib plus fulvestrant

The combination of abemaciclib 150 mg BID and fulvestrant is approved for use in HR+, HER2- MBC with a well-characterized efficacy and safety profile. In MONARCH 2 (Sledge et al. 2017), this combination exhibited a manageable safety profile and resulted in clinically meaningful PFS and OS benefit compared to fulvestrant/placebo (Verzenio package insert, 2019; Verzenios SmPC, 2018).

2. Arm B: placebo plus fulvestrant

Fulvestrant as the control arm reflects an acceptable treatment option per ESMO and NCCN guidelines (Cardoso et al. 2020; NCCN 2021).

Hematology, hepatic, and renal function tests are regularly monitored throughout the study with increased frequency in the early cycles when toxicity risks are highest. Increased susceptibility to infection will be monitored through regular hematology monitoring. These activities enable appropriate investigator oversight including the identification and management of AEs.

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

Study Procedures

A detailed schedule of study procedures and activities is presented in Section 1.3.

Participants will undergo regularly scheduled blood draws by venipuncture, which is a common clinical practice with low risks of risk of complications such bleeding, vascular or soft tissue injury, and infection (Buowari 2013).

Participants will undergo regularly radiologic imaging. The investigator, in conjunction with guidance provided in Section 1.3, will select the most appropriate imaging study. Radiologic imaging is standard practice. Risks of imaging include low levels of radiation exposure and potential allergic reactions to intravenous contrast (Sammet 2016; Garcia et al. 2017).

Tumor biopsy is … ….≥(’-(-.z ’• ○.6(..(’ …”“z (≥’ ≤ ..’ . Common risks include injury of soft tissues, vascular tissues, and infections. According to the ASCO 2019 guidelines, this is considered low risk (Levit et al. 2019).

2.3.2. Benefit Assessment

All participants will receive a known active therapy for HR+, HER2- MBC, either abemaciclib or fulvestrant. Both abemaciclib and fulvestrant are approved as single agents for the treatment of MBC (abemaciclib and fulvestrant package inserts). Treatment with abemaciclib plus fulvestrant may result in improved clinical benefit compared to fulvestrant plus placebo.

Based on known data, treatment with the combination of abemaciclib and fulvestrant is expected to be well tolerated and to delay disease progression. Prolonged disease control may also delay the need for cytotoxic chemotherapy.

2.3.3. Overall Benefit Risk Conclusion

The potential risks of the abemaciclib plus fulvestrant combination are justified in consideration of the measures to minimize these risks and the anticipated benefit of improved disease control, as measured by improved PFS in participants with HR+, HER2- MBC, an incurable disease with a poor prognosis and limited non-cytotoxic therapeutic options.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To compare the efficacy of fulvestrant with or without abemaciclib	PFS as determined by investigator assessment using RECIST 1.1
Secondary	
To further compare the efficacy of fulvestrant with or without abemaciclib	• OS • PFS by BICR • ORR • CBR • DCR • DoR
To further characterize the safety profile of abemaciclib in combination with fulvestrant	Safety – including but not limited to TEAEs, SAEs, deaths, and clinical laboratory abnormalities
To compare PRO measures of fulvestrant with or without abemaciclib	• Time to worsening in worst pain via the mBPI-SF worst pain item • Time to deterioration in physical function via the EORTC IL-19
To characterize the pharmacokinetics (PK) of abemaciclib in combination with fulvestrant	Concentrations of abemaciclib
Exploratory	
To assess exploratory clinical parameters of fulvestrant with and without abemaciclib	CCI

Objectives	Endpoints
To explore other PRO and HRQoL parameters of fulvestrant with and without abemaciclib	CCI
To assess the relationship between biomarkers and clinical outcomes	• Outcomes such as clinical efficacy and safety, and/or exposure parameters

Abbreviations: AE = adverse event; BICR = blinded independent central review; CBR = clinical benefit rate; CCI CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC IL-19 = European Organisation for Research and Treatment of Cancer Item Library 19; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-Of-Life Questionnaire Core 30; EQ-5D-5L = EuroQOL 5 Dimension 5 Level; HRQoL = health-related quality of life; mBPI-SF = modified Brief Pain Inventory-short form; ORR = objective response rate; OS = overall survival; PRO = patient-reported outcome; PFS = progression-free survival; CCI RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; CCI

Primary estimand

The primary research question is: What is the difference in PFS time between Arms A vs. B following progression/relapse on prior CDK4 & 6 inhibitor-based therapy in participants with advanced/metastatic HR+, HER2- breast cancer.

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

- Population: adult participants with advanced/metastatic HR+, HER2- breast cancer after progression/relapse on prior treatment with CDK4 & 6 inhibitor-based therapy, randomized to study intervention (primary analysis population). Further details can be found in Section 5.
- Endpoint: investigator-assessed PFS in the primary analysis population, which is defined as the time from randomization until
  - first occurrence of documented disease progression per RECIST 1.1, or
  - death from any cause in the absence of documented progressive disease.
- Treatment condition: the randomized study intervention (Arms A and B) will be administered until disease progression, unacceptable toxicity, or another protocol-defined reason for study intervention discontinuation (Section 7). Further details on study interventions, including interventions, concomitant therapy, and dose modification, can be found in Section 6.

CCI


CCI

4. Study Design

4.1. Overall Design

postMONARCH is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study in participants with HR+, HER2- advanced or metastatic breast cancer. This study will enroll adults who experienced disease progression on a CDK4 & 6 inhibitor and an AI in the first-line setting or relapse on/after CDK4 & 6 inhibitor with ET in the adjuvant setting.

Approximately 350 participants will be equally randomized between 2 treatment arms and will be treated until disease progression or other discontinuation criteria are met (Section 7).

- **Arm A:** abemaciclib plus fulvestrant
  - abemaciclib 150 mg orally BID on Days 1-28 of each cycle
  - fulvestrant 500 mg IM on C1D1 and C1D15, then on Day 1 of Cycle 2 and beyond
- **Arm B:** placebo plus fulvestrant
  - placebo BID on Days 1-28 of each cycle
  - fulvestrant 500 mg IM on C1D1 and C1D15, then on Day 1 of Cycle 2 and beyond
- Participants will be randomized using the following stratification factors:
  - geography [redacted]
  - presence of visceral metastases (Yes versus No; visceral includes lung, liver, brain, pleural, and peritoneal involvement)
  - duration on prior adjuvant/metastatic CDK4 & 6 inhibitor-based regimen (2 levels): [redacted]

The primary efficacy measure is investigator-assessed PFS, defined as time from randomization to the first occurrence of documented disease progression per RECIST v1.1, or death due to any cause in the absence of documented progressive disease.

4.2. Scientific Rationale for Study Design

Rationale for study design

The overall rationale for the study design is described in Study Rationale (Section 2.1) and in the Statistical Considerations (Section 9) sections. Dose selection details can be found in Section 6.1.

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if the relevant data are collected.

4.3. Justification for Dose

4.3.1. Abemaciclib

For the approved indication in HR+, HER2- MBC, the recommended starting dose of abemaciclib in combination with fulvestrant is 150 mg BID. This is based on the Phase 3 study, MONARCH 2 (Sledge et al. 2017), in which abemaciclib 150 mg BID in combination with fulvestrant exhibited a manageable safety profile and resulted in clinically meaningful PFS and OS benefit compared to fulvestrant/placebo in patients with HR+, HER2- advanced or metastatic breast cancer (Verzenio package insert, 2019; Verzenios SmPC, 2018).

4.3.2. Fulvestrant

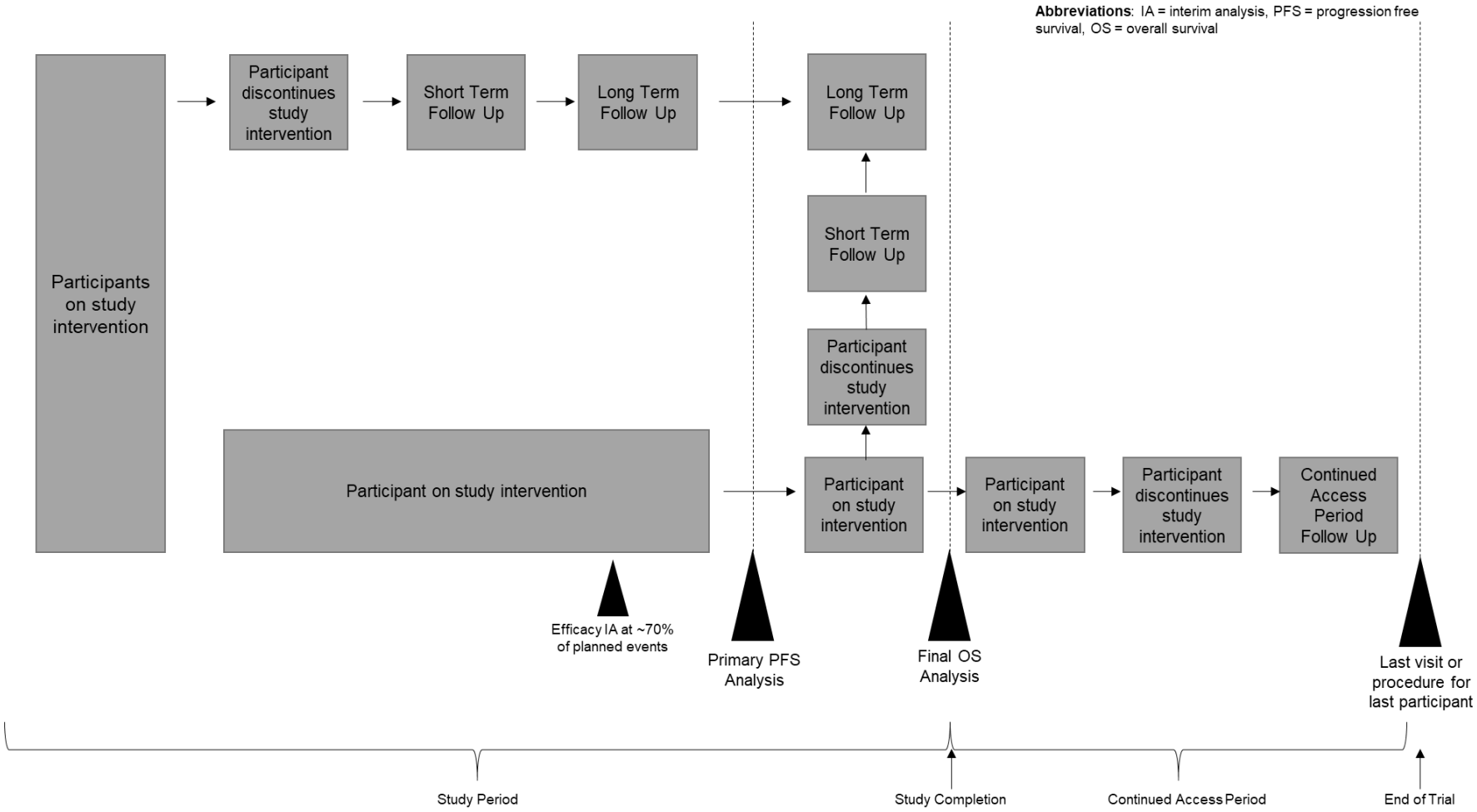
In clinical studies of participants with breast cancer, no clinically relevant PK drug interactions were observed between abemaciclib and fulvestrant. Therefore, the recommended dose of fulvestrant in combination with abemaciclib is consistent with the approved monotherapy dose of fulvestrant. Accordingly, study participants in postMONARCH will receive fulvestrant 500 mg IM on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond according to the dosing information provided in the approved local label.

4.4. End of Study Definition

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the evaluation of final OS data (see Study Period and Continued-Access Period Diagram below) as determined by the Sponsor. Investigators will continue to follow the study schedule for all participants until notified by the Sponsor that study completion has occurred.

V ≥(–(’z○(.–.. ((”.(≥z .(. –(”.(œz (’ ’((œz (≤”.≥ ○≥(≤.≥ .(– (”.(œz (zrticipant. The end of trial occurs after study completion and after the last participant has discontinued study treatment and completed continued-access period follow-up (figure below).

Study Period and Continued-Access Period Diagram



Abbreviations: IA = interim analysis; OS = overall survival; PFS = progression-free survival.

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. 18 years of age (or of an acceptable age according to local regulations, whichever is older) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Have a diagnosis of HR+, HER2- breast cancer. To fulfill the requirement of
    a) **HR+ disease:** must express, by immunohistochemistry (IHC), at least 1 of the hormone receptors (estrogen receptor [ER] or progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).
    b) **HER2- disease:** must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization as defined in the relevant ASCO/CAP Guidelines (Wolff et al. 2018).
3. Have either advanced disease not amenable to curative surgical treatment or metastatic disease.
4. Have radiologic evidence of disease progression or recurrence either
    a) On treatment with a CDK4 & 6 inhibitor (palbociclib, ribociclib, or abemaciclib) plus AI as initial therapy for advanced disease, or
    b) On/after treatment with a CDK4 & 6 inhibitor (palbociclib, ribociclib, or abemaciclib) plus ET administered as adjuvant therapy for early-stage breast cancer.
5. Have either measurable disease or non-measurable but evaluable disease. Measurable, non-measurable, and evaluable disease are defined according to the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1 [v1.1], Eisenhauer et al. 2009).
6. Have a performance status (PS) of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982).
7. Must be deemed appropriate for treatment with ET.

8. Have discontinued previous treatments and recovered from the acute effects of therapy to at least Grade 1, except for residual alopecia and peripheral neuropathy, with the following therapy washout periods required prior to receiving study drug:

Previous Treatment	Length of Time Prior to First Dose of Study Drug
CDK4 & 6 inhibitor	7 days4
Endocrine therapy	days or 5 half-lives, whichever is shorter4
Radiotherapy	days
Major surgery	14 days4

9. Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	1.5×10⁹/L
Platelets	100×10⁹/L
Hemoglobin	8 g/dL
Note: z – ’ ((’ ≤ . z . (z(z ’… (”. • “○ • ’ (or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug.	
Hepatic	
Total bilirubin	<8D n e g i z ’≤ z (’ ”(Y’ • … (≥ • . (. ’ ”(z(z (• ’ ♂ • ’ (A8 ×ULN and direct bilirubin within normal limits are permitted
ALT and AST	3×ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; G-CSF = granulocyte colony-stimulating factor; ULN = upper limit of normal.

Sex and Contraceptive/Barrier Requirements

Sex

10. Males and females may participate.

a. **Male participants**
Must agree to use hormone suppression (received monthly and initiated at least 28 days prior to Cycle 1 Day 1) with a gonadotropin-releasing hormone agonist such as goserelin or leuprolide.

b. **Female participants**
Must have postmenopausal status due to either surgical/natural menopause or ovarian suppression (received monthly and initiated at least 28 days prior to Cycle 1 Day 1) with a gonadotropin-releasing hormone agonist, such as goserelin or leuprolide.
Postmenopausal status due to surgical/natural menopause requires at least 1 of the following:
    a. prior bilateral oophorectomy

b. z“.(. 55 years and amenorrhoeic for at least 12 months or with a diagnosis of menopause
c. age C; and <55 years, amenorrhoeic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression), and FSH in the postmenopausal range (C; (● ln :● e 3

Contraceptive/Barrier Requirements

11. Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants

No male contraception is required except in compliance with specific local government study requirements. Males are eligible to participate if they agree to refrain from donating sperm during the treatment period. Contraception requirements for male participants receiving fulvestrant should follow the approved local label.

b. Female participants

Women of childbearing potential (WOCBP) must test negative for pregnancy prior to initiation of treatment with a negative serum pregnancy test at the screening visit, followed by a negative urine pregnancy test within 48 hours prior to first exposure to study drug, and

WOCBP should use highly effective contraception (less than 1% failure rate) to prevent pregnancy while receiving study treatment and for 3 weeks after the last dose of blinded study drug and for 2 years after the last dose of fulvestrant (or according to local approved fulvestrant label).

Note: WOCBP who are completely abstinent or in a same-sex relationship as part of their preferred and usual lifestyle must agree to either remain abstinent or refrain from sexual intercourse with males.

Please refer to Section 10.4 (Appendix 4) for definitions and additional guidance related to contraception.

Informed Consent

12. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusions

13. Willing to participate for the duration of the study and to follow study procedures including use of Sponsor-provided electronic devices to collect patient reported outcomes
14. Able to swallow capsules and tablets

5.2. Exclusion Criteria

Participants are excluded if any of the following apply:

Medical Conditions

15. Have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.
16. Have symptomatic or untreated central nervous system (CNS) metastasis. Participants with treated CNS metastases are eligible if
    a. [illegible] prior to first dose of study treatment, and
    b. they have not received corticosteroids and/or anticonvulsants for at least 14 days prior to first dose of study treatment, and
    c. their disease is both asymptomatic and radiographically stable by repeat imaging for at least 28 days prior to consent (repeat imaging should be performed during study screening).
17. Have a history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Exception: patients with controlled atrial fibrillation for >30 days prior to randomization are eligible.
18. Have serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment [for example, estimated creatinine clearance <30 mL/min], active symptoms of ILD/pneumonitis, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection [illegible] or a preexisting chronic condition resulting in clinically significant diarrhea).
19. Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years
20. Have a known active systemic infection (for example, bacterial, fungal, or detectable viral infection requiring systemic therapy).
    a) Participants with uncontrolled human immunodeficiency virus (HIV) infection or an acquired immunodeficiency syndrome (AIDS) defining illness are not eligible. Participants with known HIV infection and CD4+ T-[illegible] cells/µL are eligible.
    b) Participants with hepatitis B are not eligible unless viral load is below the level of quantification.
    c) Participants with known hepatitis C are not eligible unless they have completed curative anti-viral therapy and viral load is below the level of quantification.
    d) Screening for HIV, coronavirus disease 2019 (COVID-19), hepatitis B, or hepatitis C is not required.

Prior/Concomitant Therapy

21. Have received any intervening line of systemic therapy between disease recurrence/progression and study screening.
22. Have received more than 1 line of therapy for advanced or metastatic disease.
23. Have received prior treatment with chemotherapy for MBC.
24. Have received prior treatment with any CDK4 & 6 inhibitor-based regimen other than those specified. Prior treatment with a CDK4 & 6 inhibitor in more than 1 setting (e.g., adjuvant and then metastatic) is not permitted.
25. Have received prior treatment with fulvestrant, any investigational ER-directed therapy (including SERDs and non-SERDs), any PI3K-, mTOR-, or AKT-inhibitor.
26. Have known pathogenic germline mutations appropriate for a PARP inhibitor, in regions where these therapies are approved and available
27. Have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents (e.g. denosumab) <7 days prior to randomization.
28. Are receiving concurrent exogenous reproductive hormone therapy (for example, birth control pills, hormone replacement therapy, or megestrol acetate). Appropriate washout (for example, applying 7 days or 5 times the half-life elimination rule). Note: topical vaginal estrogen therapy is permitted if all other non-hormonal options are exhausted.
29. Have received an autologous or allogeneic stem cell transplant.

Prior/Concurrent Clinical Study Experience

30. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other Exclusions

31. Are pregnant or breastfeeding.
32. Have known or suspected hypersensitivity reactions or intolerance to study drug or to any of the excipients (e.g., lactose), unless deemed appropriate by the investigator.

5.3. Lifestyle Considerations

Participants should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to their effect on cytochrome P450 (CYP)3A4.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate but are not subsequently randomized to a study treatment due to inability to complete or meet the participation criteria (Sections 5.1 and 5.2) within the 28-day baseline screening period. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Patients who are ≥…. ● ’ .≧((• .(.≤ ….(–z’○ …(≤z (• .(…≤ ….…≧(z (z (’ … z◑ –(≺(….×8(
Patients may be rescreened up to 2 times. Each time rescreening is performed, the patient must sign a new ICF and will be assigned a new identification number. All required tests (see SoA, Section 1.3) must be repeated for patients who are rescreened in a new 28-day baseline screening, unless approved by the Sponsor CRP/CRS.

If initial laboratory screening result did not meet eligibility criteria, for example absolute neutrophil count (ANC) was too low, then the test can be repeated within the 28-day screening period to confirm eligibility without being considered a screening fail. However, laboratory tests may not be repeated more than twice.

The following patients may be eligible for rescreening:

- patients who have become eligible to enroll in the study as the result of a protocol amendment
- patient status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again, and
- patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as severe weather, death in family, child illness).

The investigator should contact the Sponsor CRP prior to rescreening a patient.

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

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal product(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

	Arm A		Arm B	
Treatment	**Abemaciclib**	**Fulvestrant**	**Placebo**	**Fulvestrant**
Dose	150 mg	500 mg	Matched to abemaciclib	500 mg
Route	PO	IM	PO	IM
Schedule	BID on Days 1-28 of each cycle	C1D1 and C1D15, then on Day 1 of Cycle 2 and subsequent cycles	BID on Days 1-28 of each cycle	C1D1 and C1D15, then on Day 1 of Cycle 2 and subsequent cycles
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization	Authorized and not used according to EU authorization	Not authorized in EU	Authorized and not used according to EU authorization

Abbreviations: BID = twice daily; C = cycle; D = day; IM = intramuscular; mg = milligrams; PO = orally.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Selection and Timing of Doses

A cycle is defined as an interval of 28 days. The 28-day cycle length should be maintained throughout the treatment phase regardless of dose interruptions. Participants will begin dosing assigned treatment on C1D1. Every attempt should be made to maintain a 28-day +/- 7-day cycle for fulvestrant administration. When delays are required, doses should be resumed at earliest medically appropriate opportunity based on investigator judgment. Additional clinic visits may be required for administration.

Treatment will continue until progression, unacceptable toxicity, or other discontinuation criteria are met (Section 7.1).

In addition to the permitted protocol windows (see SoA, Section 1.3), a maximum of 7 days delay of a cycle start due to holiday, weekend, bad weather, or other unforeseen circumstances, but not due to AE, will be permitted and not counted as a protocol deviation. In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Sponsor CRP/CRS. Response assessments should remain on the original schedule (see SoA, Section 1.3).

6.1.2. General Dosing Instructions

Assignment to either abemaciclib (Arm A) or placebo (Arm B) will be blinded to investigators and participants. Blinded study drug will be administered at a starting dose of 150 mg twice daily, and it is provided as 50 mg tablets. Blinded study drug should be taken twice daily (with at least approximately 6 hours separating doses) at the same time each day with 6-8 ounces of water. Participants should be instructed to swallow tablets whole and not chew or crush them.

In rare circumstances, if an investigator clinically determines and documents that it is in the best interest of the patient to start at a dose of blinded study drug lower than 150 mg BID, the investigator may consult with the Sponsor CRP/CRS and request approval. If the initial reduced dose is tolerated, then subsequent dose escalation is encouraged and should be discussed with the Sponsor CRP/CRS for approval.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate 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.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer 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.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

Investigators should consult the study drug information provided in the protocol, Investigator's Brochure, or label for the specific administration information (including warnings, precautions, contraindications, and adverse reactions).

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized at a ratio of 1:1 to Arms A and B. Randomization will be stratified by the following 3 factors:

- Geography (3 levels)


CCI

- Presence of visceral metastases (2 levels)
  - Yes, or
  - No
- Duration on prior adjuvant/metastatic CDK4 & 6 inhibitor-based regimen (2 levels)

CCI

Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Upon obtaining informed consent, site personnel should access the IWRS, which will assign a patient number. Participants who meet all criteria for enrollment will be randomly assigned to treatment.

Arms A and B will be blinded to participants and investigators.

The Sponsor will collect and store all tumor images throughout the study. An independent review of imaging measurements will be performed by an independent panel of radiologists. In addition, a secondary PFS analysis based on independent central review will be conducted.

Participants randomized to the control group (Arm B) will not be permitted to cross over to the experimental group (Arm A). If a participant discontinues study treatment and knowledge of the participant's treatment assignment is deemed essential to the selection of the participant's next treatment regimen, the investigator may consult with the Sponsor CRP/CRS and request unblinding to guide further post-discontinuation therapies. There are no restrictions to post-discontinuation therapy.

Interim analyses for safety and efficacy/futility will be conducted under the guidance of an independent data monitoring committee (DMC). Refer to Section 10.1.5 for additional details.

For safety and efficacy/futility analyses assigned to the DMC, only the designated Statistical Analysis Center (SAC), which is independent of the Sponsor, will perform analyses on unblinded data, that is, an aggregate database with actual treatment assignments. At the request of the Sponsor, the SAC may provide pooled summary reports to the Sponsor (for example, a summary of AEs across the study). These reports will not include treatment arms.

Early access to PK Data

To support timely exposure-response analyses, PK analyses will be conducted prior to the first efficacy interim analysis. Periodic transfers for review of data relevant to PK analyses, including dosing and bioanalytical results, will be performed. An early PK analysis will be performed when the majority of treated participants have completed their final PK sample collection visit, and prior to the first efficacy interim analysis. This early PK analysis will be performed by an independent team of PK analysts, and the results will not be shared with the study team until the trial is fully unblinded. Protocols will be in place to maintain the blind, including the use of

- separate restricted data containers
- aliased patient identifiers (IDs), and

datasets containing data required for population PK analysis only (specifically, no efficacy data).

6.3.1. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding [illegible] always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor CRP/CRS prior to [illegible] the Sponsor must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. This option may be used [illegible] assignment.

All calls resulting in an unblinding event are recorded and reported by the IWRS.

If the investigator or participant becomes unblinded, that participant will be discontinued from study intervention and will undergo post-discontinuation follow-up. Long-term follow-up procedures will be followed until death, loss of follow-up, withdrawal of consent, or study completion. In cases in which there are ethical reasons for the participant to remain on the study intervention in the event of unblinding, the investigator must obtain specific approval from the Sponsor CRP/CRS for the participant to continue in the study.

6.3.2. Inadvertent Unblinding

Every effort will be made to blind both the participant and the investigator to the identity of the treatment, but the inadvertent unblinding of a participant may occur. If an investigator, site personnel, or participant is inadvertently unblinded, the unblinding will not be sufficient cause for the participant to be discontinued from study intervention or excluded from study analyses. In cases in which there are ethical reasons for the participant to remain on the study intervention in the event of unblinding, the investigator must obtain specific approval from the Sponsor CRP/CRS for the participant to continue in the study.

6.4. Study Intervention Compliance

6.4.1. Blinded Study Drug

The number of blinded study drug tablets dispensed to and returned by each participant must be maintained, reconciled, and recorded at each applicable clinic visit. Compliance will be assessed at each applicable clinic visit by direct questioning and counting of the returned tablets/capsules. These counts must be recorded in the source documents and CRF.

From Cycle 1 Day 1 to Cycle 3 Day 1, participants will also complete a paper Patient Dosing Diary to record the exact time and date of study drug doses, which will be utilized in PK assessments. This paper diary is not intended to monitor compliance.

Start and stop dates, including dates for doses withheld, reductions, and/or re-escalations will be recorded in the CRF.

A participant ● (z×.(. 75% of the planned doses to be deemed compliant. Similarly, participant may be considered noncompliant if he or she is judged by the investigator to have ’ … ’ z∞ ((….z .≥○ (z×…(<AD’ (–(”.(. ∝z .≥(≥ …(–(≥ (≥ “(’ (z(≤ ≤○8

6.4.2. Fulvestrant

Fulvestrant will be administered under medical supervision by the investigator or designee. The investigative site will record the date, time, and dose in the source documents and CRF. The site will also record any dose adjustments and reason for adjustment. If the dose was not administered, the site will document the reason.

6.5. Dose Modification

In exceptional cases of planned delays (including but not limited to vacation or holidays), additional study drug may be dispensed.

When treatment is delayed, if possible and appropriate, patients should resume within the same treatment cycle. If not possible, then every effort should be made to resume on the first day of the next scheduled cycle. In rare circumstances, if the participant has clinical benefit without disease progression and is recovering from toxicity, a delay of >28 days may be permitted. Such circumstances must be discussed with the Sponsor CRP/CRS. All dose modifications should be documented, including a clear rationale for the modification.

U .(. … ’ (AG(≥z (● (•.(≥’ ≤ .≥(’ ”(”.(Sponsor CRP/CRS.

6.5.1. Blinded Study Drug

Management of some adverse reactions may require dose interruption and/or dose reduction. When dose reduction is necessary, decrease the dose by 50 mg at a time. Discontinue blinded study drug for patients unable to tolerate 50 mg BID. If blinded study drug must be discontinued, a participant may continue to receive fulvestrant.

Refer to the tables below for further details on dose modification and management.
Dose Reduction Guidelines

Dose Adjustment	Blinded Study Drug Dose	Frequency
Starting dose	150 mg	BID
First dose reduction	100 mg	BID
Second dose reduction	50 mg	BID

Abbreviation: BID = twice a day.

6.5.1.1. Blinded Study Drug Dose Adjustments for Treatment-Emergent, Related* Adverse Events

The table below provides guidance for the management of treatment-emergent, related (i.e., with reasonable causal relationship with blinded study drug) AEs. An investigator may use discretion and suspend or reduce doses without meeting one of the criteria below and this would not be considered a protocol deviation, though rationale should be documented.

*Related means there is a reasonable causal relationship with blinded study drug.

Toxicity Type	Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 1 or 2	Not required	
	Grade 3	Suspend until toxicity resolves to Y z≥.(A	Not required
	Recurrent Grade 3, or Grade 4	Suspend until toxicity resolves to Y z≥.(A	Resume at next lower dose level
Patient Requires Blood Cell Growth Factors Additional guidance for use of growth factors is in Section 6.8.1	Regardless of severity	Suspend until toxicity resolves to at least Grade 2 and a minimum of 48 hours after growth factor administration	Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor (that is, a second dose reduction not required)
Nonhematologic Toxicity Excluding Diarrhea, ALT/AST Increased, Interstitial Lung Disease/Pneumonitis, and VTE (see below) Additional guidance for renal monitoring is in Section 8.2.4 and for VTE Section 8.2.5.	Grade 1 or 2	Not required	
	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1 or Grade 3 or 4	Suspend until toxicity resolves to baseline or Grade 1	Resume at next lower dose level
Diarrhea Additional guidance for diarrhea management is in Section 6.8.3.	Grade 1	Not required	
	Grade 2 that does not resolve to Y z≥.(≤ within 24 hours	Suspend until toxicity resolves to Y z≥.(≤	Not required

Toxicity Type	Severity	Dose Suspension	Dose Reduction
	Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures or Grade 3 or 4 or Requires hospitalization	Suspend until toxicity resolves to Y z≥.(≤	Resume at next lower dose level
ALT/AST Increased See Section 8.2.3 for additional guidance for hepatic monitoring and Section 8.2.3.1 for special hepatic safety data collection.	Grade 1 or 2	Not required	
	Persistent or recurrent Grade 2, or Grade 3	Suspend until toxicity resolves to baseline or Grade 1	Resume at next lower dose level
	Y z≥.(Awith total bilirubin >2×ULN, in the absence of cholestasis, or Grade 4	Discontinue blinded study drug	
VTE Additional guidance for VTE monitoring is in Section 8.2.5.	Grade 1 or 2	Not required	
	Grade 3 or 4	Suspend and treat. Resume when the patient is clinically stable	Not required
Interstitial Lung Disease/Pneumonitis Additional guidance for ILD/pneumonitis monitoring is in Section 8.2.6.	Grade 1 or 2	Not required	
	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days.	Suspend until toxicity resolves to baseline or Y z≥..1	Resume at next lower dose level
	Grade 3 or 4	Discontinue blinded study drug	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ILD = interstitial lung disease; ULN = upper limit of normal; VTE = venous thromboembolic event.

Note: Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within 8 weeks (as measured from the stop date of the first event). As general guidance, for a participant who experiences a new episode of Grade 3 hematological toxicity more than 8 weeks from a previous episode of the same Grade 3 toxicity, the investigator may consider resuming the same dose if the participant satisfies the following conditions:

s z• ○(.”..● z ○ “’≤z○(≤ (2Y z≥.(. A3(≥ ’ “(”z (’● ..frame

absence of serious infections
ongoing benefit

6.5.1.2. Re-escalation Criteria for Blinded Study Drug

If the blinded study drug dose is reduced for an apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the [illegible] escalated to the prior dose level, at the discretion of the investigator and after consultation with the Sponsor CRP/CRS. Re-escalation to the prior dose level will be permitted only once. After re-escalation, subsequent dose adjustments should be based on the dose that the patient is currently receiving.

6.5.2. Fulvestrant

Fulvestrant dose adjustments will be determined by the investigator in accordance with the approved product labels. Dose may be re-escalated at the discretion of the investigator and after consultation with the Sponsor CRP/CRS. For patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection. In the event that fulvestrant must be discontinued, a participant may continue to receive blinded study drug.

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

After study completion (see Section 4.4), patients who are on study treatment and eligible for the continued-access period will be unblinded.

Patients receiving study treatment and experiencing clinical benefit may continue to receive study treatment in the continued-access period until any of the criteria for discontinuation is met (Section 7). Placebo will no longer be administered. The continued-access period will apply only if at least 1 patient is receiving study intervention at study completion. The Sponsor will notify investigators when the continued-access period begins. The Sponsor may allow patients to enroll [illegible]-term continued access.

The continued-access period will begin after study completion and ends at the end of the study (Section 4.4). Continued-access follow-up will begin when the patient and the investigator agree to discontinue study treatment. Follow-up procedures will be performed as in the SoA (Section 1.3).

Patients 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.

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

Investigators will perform standard procedures and tests. The choice and timing of the tests will [illegible] The Sponsor will not routinely collect the results of these assessments.

6.7. Treatment of Overdose

In case of overdose, use supportive therapy. There is no known antidote for abemaciclib overdose.

In the event of an overdose, the investigator/treating physician should

- contact the Medical Monitor immediately
- evaluate the participant to determine, in consultation with the Sponsor CRP/CRS, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities
- obtain a plasma sample for PK analysis following overdose if requested by the Medical Monitor (determined on a case-by-case basis), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Concomitant Therapy

Documentation of all premedications, supportive care, and concomitant medications must be captured at each visit in the eCRFs. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that the patient receives at enrollment, during the study, and after the last dose of study treatment at the short-term follow-up visit (see SoA, Section 1.3) must be recorded along with the

- reason for use, and
- dates of administration, including start and end dates.

The Sponsor CRP/CRS should be contacted for any questions regarding concomitant or prior therapy.

6.8.1. Palliative and Supportive Care

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

Palliative radiation therapy is permitted for small areas of painful metastases that cannot be managed adequately using systemic or local analgesics after agreement of the Sponsor CRP/CRS. Such areas must not be a target lesion and must not meet RECIST v1.1 criteria for progressive disease. Any symptomatic deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific antitumor systemic therapy, will be cause for discontinuation of study therapy.

Use of granulocyte-colony stimulating factor, prophylactic antibiotics, erythropoietin, and blood product transfusions is allowed according to ASCO and ESMO guidelines (Rizzo et al. 2008; Crawford et al. 2009; Flowers et al. 2013; Smith et al. 2015)

6.8.2. Bisphosphonates and RANK-L Targeted Agents

Patients with bone metastases present on baseline imaging should be appropriately treated with bisphosphonates or RANK-L targeted agents, for example, denosumab, per respective approved labels. Initiation of treatment with bone-modifying agents must begin at least 7 days prior to randomization. Patients receiving bisphosphonates or RANK-L targeted agents should not switch treatments, for example, replacing bisphosphonate with denosumab, while on study treatment. However, exceptional cases without evidence of disease progression may be considered in consultation with the Sponsor CRP/CRS. These exceptional cases will not incur a protocol deviation.

6.8.3. Supportive Management for Diarrhea

It is important that all participants receive instructions for the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include

At the first sign of loose stools, the patient should begin antidiarrheal therapy (for example, loperamide) and communicate with site personnel for further instructions and follow-up.
Patients should also be encouraged to drink at least 64 ounces (approximately 2000 mL) fluids per day.
Site personnel should assess patient within 24 hours.
Follow dose-modification guidance for blinded study drug in Section 6.5.1.1, including dose suspension and/or reduction as appropriate.
For severe diarrhea, or diarrhea associated with nausea or vomiting, consider

- IV fluids with electrolyte replacement
- measurement of absolute neutrophil counts
- monitor patients for fever.

If diarrhea is associated with fever or severe neutropenia, consider broad-spectrum antibiotics.

6.8.4. Concomitant Therapy

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

6.8.4.1. Modulators of CYP3A

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

coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (AUC) of abemaciclib by 3.4-fold (Study I3Y-MC-JPBE), and
coadministration of rifampin, a strong CYP3A inducer, decreased exposure of 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 (Appendix 6, Section 10.6). This includes grapefruit or

grapefruit juice. In particular, avoid oral administration of the very strong CYP3A inhibitor, ketoconazole.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of blinded study drug by 50 mg at the start of CYP3A inhibitor treatment. That is, for patients receiving 150 mg twice daily, reduce the dose to 100 mg twice daily. For patients who have already had dose reduced to 100 mg twice daily for tolerability, reduce the dose further to 50 mg twice daily. Alternatively, the investigator may consider suspending blinded study drug for the duration of the CYP3A inhibitor medication (see Section 6.5).

Upon discontinuation of the strong CYP3A inhibitor, the dose of blinded study drug may be re-escalated to the dose that was used before starting the strong inhibitor after a sufficient washout period (3 to 5 half-lives of the strong inhibitor). Re-escalation of the blinded study drug dose requires review and approval from the Sponsor CRP/CRS.

Inducers of CYP3A should be substituted or avoided if possible (Appendix 6, Section 10.6). T z≥● ’ ’ z ’ (’ ”(z(Tr i BR(’ ≥ ≤..(AG(≥z (● (•.(≥’ ≤ .≥.(’ ”(”.(Sponsor CRP/CRS.

6.8.4.2. **Transporter Substrates**

Abemaciclib inhibits the transporters P-glycoprotein, breast cancer resistance protein, organic cation transporter 2, 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.

6.8.5. Medications and therapies not permitted

With the exceptions listed in the sections below, therapies for cancer (including specifically aromatase inhibitors, anti-estrogens other than fulvestrant, chemotherapy, and immunotherapy) will not be permitted while patients are on study treatment. Use of megestrol acetate as an appetite stimulant is not permitted due to anti-estrogen effects.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will move into the post-discontinuation follow-up period. See the SoA for data to be collected and for any further evaluations that need to be completed.

A participant should be permanently discontinued from study intervention if the participant or ”.(. z ’≤’ z (≥…”“ ..(..quests to discontinue the study intervention

In addition, participants will be discontinued from the study intervention in the following circumstances:

The participant becomes pregnant during the study. Refer to Section 8.3.2 for additional guidance.
The participant has evidence of progressive disease.
The participant experiences unacceptable toxicity.
The participant is significantly noncompliant with study procedures and/or treatment.
The investigator decides that the participant should be discontinued.
The participant, for any reason, requires treatment with another therapeutic agent with demonstrated efficacy for the study indication. Discontinuation from study intervention will occur prior to introduction of the new agent.
The participant enrolls in another clinical study judged not to be scientifically or medically compatible with this study.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

at any time at his/her own request
at the request of his/her designee (for example, legal guardian)
at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

When applicable, and if possible, an early discontinuation visit should be conducted. See SoA for data to be collected and any further evaluations that need to be completed. The participant will be permanently discontinued from all study interventions and the study at that time.

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

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she 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 unable to be followed.

Within legal and ethical boundaries, study site personnel or an independent third party will attempt to collect the survival status for all randomized participants who are lost to follow-up, including those who do not receive study treatment. Public sources may be searched for survival status information. The survival status will be documented, and the participant will not be considered lost to follow-up if survival status is determined.

Sponsor personnel will not be involved in any attempts to collect survival status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Immediate safety concerns should be discussed with the Sponsor 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.

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

8.1. Efficacy Assessments

8.1.1. Efficacy Assessments at Baseline and during Study Treatment

Imaging studies (CT, including spiral CT, or MRI scan of the chest, abdomen, and pelvis) will be performed locally per the SoA (Section 1.3). It is recommended that whenever possible, CT imaging of the abdomen and pelvis be performed with IV contrast. For patients with CT contrast hypersensitivity, a CT scan of the chest without contrast and gadolinium-enhanced MRI of the abdomen are encouraged. The CT portion of a PET-CT may be used for response assessment if the site can document that the CT is of identical quality to a diagnostic CT (with IV and oral contrast). A PET scan alone, or as part of a PET-CT, cannot be used to assess response according to RECIST v1.1.

Bone scintigraphy will be performed at baseline and repeated per the SoA (Section 1.3). Bone scans should be repeated for suspicion of either a CR in target disease or bone progression. For patients with new lesions on post-baseline bone scintigraphy, targeted assessment by X-ray, CT scan with bone windows, or MRI should be performed to confirm findings.

For patients with treated brain metastases, brain MRI with contrast is preferred; however, if contraindicated, then MRI without contrast or a CT with/without contrast is acceptable. Imaging should be performed at the RECIST response assessment intervals per the SoA (Section 1.3).

For patients with RECIST non-measurable bone-only disease and lesions identified on baseline bone scintigraphy that are not visible on the chest, abdomen/pelvis CT or MRI, all such lesions will be evaluated by directed imaging (X-ray, CT scan with bone windows, or MRI) to enable serial assessment. Directed imaging will be performed per the SoA (Section 1.3).

For patients with locoregionally recurrent breast cancer not amenable to curative treatment, breast MRI will be performed per the SoA (Section 1.3).

For patients with visible tumor (such as skin lesions), photography will be performed. Each image of the tumor should include a ruler, patient identification, and the date. Photography should be performed per the SoA (Section 1.3). New skin lesions should be photographed.

For patients in the continued-access period (after study completion), efficacy assessments (frequency and type) will be at the discretion of the investigator.

8.1.2. Efficacy Assessments during Post-Discontinuation Follow-Up

Post-discontinuation follow-up is described in the SoA (Section 1.3). For randomized patients who never received study treatment or those who discontinued without objectively measured PD, the investigative sites will continue to monitor patients. Tumor response should be assessed approximately every 8 weeks for 12 months relative to Cycle 1 Day 1 and thereafter approximately every 12 weeks until the patient has objective disease progression, death, or study completion. In addition, anticancer therapies initiated after study treatment discontinuation will be collected during this follow-up period.

After the patient experiences first objective disease progression, radiologic imaging and photographic images are no longer required. The patient will be followed approximately every 12 weeks until the death or overall study completion. The Sponsor will continue to collect survival data on all patients but may reduce data collection for other efficacy data. Sponsor will notify investigators when reduced data collection can begin.

8.1.3. Primary Efficacy Measure

Response Evaluation Criteria in Solid Tumors v1.1 (Eisenhauer et al. 2009) will be applied for tumor response and progression. The method used at baseline must be consistent throughout the study. Local imaging (investigator assessment with site radiological reading) will be used.

Sponsor, or its designee, will collect and store tumor assessment images to permit a blinded independent central review. Please see the Site Imaging Manual for guidelines on how imaging studies should be performed.

For patients with non-measurable, bone-only disease (refer to Inclusion Criterion [5]), objective progression will be established if at least 1 of the following criteria is met:

the appearance of 1 or more new lesions (in or outside of bone), or
unequivocal progression of existing bone lesion(s).

According to RECIST v1.1, the finding of a new lesion should be unequivocal and not attributable to findings thought to represent something other than tumor (for example, some … (• .(Ω..’ (● z (•.(.’● ○(”.z♂ “((–z .(.–(….’ ’ “(Ω..’ s). Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless at least 1 of the above criteria is met.

See Section 9.4.2 for definitions of the efficacy endpoints.

8.2. Safety Assessments

8.2.1. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any relevant changes as an AE.

The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

l ’“ ’–’≤z (z• ● z◊(◊z• z (–’ ≥’ “ (z .(.” .(. ”’≤”(z .(. (z ≤’z .≧(’ ”(”.(. ≥..○ ’ “(≥’ .z .(. (z .(,, ≥“.≧(• (”.(: … ”“z ((•.(● .(.……..(.”z (… .≦.≧(– (”.(. z ’≤’ z (≤ ≥’ ’ 8

Until the completion of V801 (inclusive of this visit), all abnormal laboratory tests considered significant should be repeated until the values return to normal, baseline, or are no longer considered clinically significant by the investigator or the Medical Monitor.

If such values do not return to normal/baseline within a period of time, the etiology should be investigated, and the Sponsor notified.

All required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and the laboratory manual.

If laboratory values from non-protocol specified assessments performed at a local laboratory require a change in participant management or are considered significant by the investigator (e.g., SAE or AE or dose modification), then this should be reported as an AE.

8.2.2. Pregnancy Testing

Perform pregnancy testing per the SoA (Section 1.3).

8.2.3. Hepatic Safety Monitoring

Close hepatic monitoring and evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	Rem((Rl m(D (n e g (Rem((Rl m(B (n e g (≤ ≤ … (’ ”(mSe(A (ULN
Rem((Rl m(<8D (n e g	Rem((Rl m(B (•z .◌ .(. ALT (Rl m(A (•z .◌ .(≤ ≤ … (’ ”(mSe(A (ULN

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, evaluation should include physical examination, a thorough medical history that includes symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications

(including over-the-counter, herbal, and dietary supplements), and history of alcohol drinking and/or other substance abuse. In addition, the evaluation should include a blood test for PT-INR; serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Sz .≥((".(. z '… ("' (z ≥(' ' ial evaluation results, further testing should be considered, in consultation with the Sponsor CRP/CRS, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine '≤ ○ " (≤ ….6(p '○ (≥' .z .6(• ○ ≥(z≤ " ◊(○…○6(' z (…" ◊("○≤ '≥.6(z ≥(• ○ ≥(" "z '≥ ○.."z ◊8Sz .≥((".(≤ ≤ ● z ≤..(z ≥(".(: …"‘z (z … ● … (–(".(. z '≤ z (≤♂ '≤z◊(≤ ≥' ' 6(".(: …"‘z (" ◊≥(≤ '≥..(.–erring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, and/or a liver biopsy.

8.2.3.1. Additional Hepatic Safety Data Collection

Additional safety data should be collected via the CRF if any of the following conditions occur:

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

V○..z ' (–(… ● (Rem((Rl m((D (n e g ((A((● .(≤ .≤ ' .(….
m".(≤ ● • ' z ' (–(.○..z .≥(Rem((Rl m(B (n e g (z ≥(.○..z .≥(mSe(A (
ULN

1 1 1 1 1 1 1 1 hco 1

V○..z .≥(Rem((Rl m(B (• z .♂ .(. (A((● .(≤ .≤tive tests
m".(≤ ● • ' z ' (–(.○..z .≥(Rem((Rl m(A (• z .♂ .(z ≥(.○..z .≥(mSe(A (
ULN

In all study participants

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

8.2.4. 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. If renal impairment is suspected per the investigator s clinical assessment, measurement of serum cystatin C on a central chemistry laboratory sample may be performed to confirm renal function.

Blinded study drug dose adjustment should follow the protocol guidance for non-hematological toxicities in Section 6.5.1.

8.2.5. Guidance for Venous Thromboembolic Events

In breast cancer, VTE has been identified as an adverse drug reaction (ADR) for abemaciclib in combination with ET. In the randomized Phase 3 studies in participants with breast cancer who received abemaciclib in combination with ET, a greater number of participants experienced VTEs in the abemaciclib plus ET arms than in the placebo plus ET arm or ET alone arm. The majority of participants who experienced VTEs were treated with anticoagulants. In studies with single-agent abemaciclib use in the metastatic breast cancer population or other tumor types, including non-small cell lung cancer, no increased rates of VTEs were observed as compared to the incidence of VTEs for these patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known.

Monitor participants for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate. Refer to Section 6.5.1 for guidance on dose adjustments of blinded study drug for patients with VTEs.

8.2.6. Guidance for Interstitial Lung Disease/Pneumonitis

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

Ask participants to report any new or worsening pulmonary symptoms, such as dyspnea, cough, and fever, and investigate and treat as per local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high-resolution CT, bronchoalveolar lavage, and biopsy as clinically indicated. Refer to Section 6.5.1 for guidance on dose adjustments or discontinuation of blinded study drug for patients with ILD/pneumonitis.

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

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

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

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

SAEs, including death, caused by disease progression or otherwise due to study disease should not be reported unless the investigator deems them to be possibly related to study treatment.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Cycles/Visits Impacted	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
	Adverse Event					
All AEs	Baseline (Pretreatment) Cycle 1 Cycle XX (Treatment Period) V801 (Short-Term Follow-Up Period) V501 V5XX (Continued-Access Period) V901 (Continued-Access Follow-Up Period)	Signing of the ICF	End of 30-day short-term post-discontinuation follow-up	As soon as possible upon site awareness	AE eCRF	N/A
	Serious Adverse Event*					
SAE and SAE updates **prior** to start of study intervention **and** deemed reasonably possibly related to study procedures	Baseline (Pretreatment)	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE eCRF	SAE paper form
All SAE and SAE updates **after** start of study intervention	Cycle 1 Cycle XX (Treatment Period) V801 (Short-Term Follow-Up Period) V501 V5XX (Continued-Access Period) V901 (Continued-Access Follow-Up Period)	Start of intervention	End of short-term follow-up	Within 24 hours of awareness	SAE eCRF	SAE paper form
All SAEs related to protocol procedures or study treatment and SAE updates	V802 V8XX (Long-Term Follow-Up)	Start of long-term follow-up	R–..(z ’≤ z (study participation has ended (that is, no longer receiving study treatment and no longer in follow-up)	Within 24 hours of awareness	SAE CRF	SAE paper form

Event	Cycles/Visits Impacted	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
SAEs related to protocol procedures or study treatment z–..(z ’≤ z (≥ (participation has ended **and** the investigator becomes aware	N/A	R–..(z ’≤ z (study participation has ended	N/A	Promptly	SAE paper form	N/A
	Pregnancy					
Pregnancy in female participants and female partners of male participants	Cycle 1 Cycle XX (Treatment Period) V801 (Short-Term Follow-Up Period) V501 V5XX (Continued-Access Period) V901 (Continued-Access Follow-Up Period)	After the start of study intervention	1 week after last dose (see Section 8.3.2 for pregnancy outcome follow-up guidance)	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	SAE paper form
	Product Complaints					
PC associated with an SAE or might have led to an SAE	Cycle 1 Cycle XX (Treatment Period) V801 (Short-Term Follow-Up Period) V501 V5XX (Continued-Access Period) V901 (Continued-Access Follow-Up Period)	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Cycle 1 Cycle XX (Treatment Period) V801 (Short-Term Follow-Up Period) V501 V5XX (Continued-Access Period) V901 (Continued-Access Follow-Up Period)	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	N/A	N/A	N/A	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A

Event	Cycles/Visits Impacted	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
PC (if investigator becomes aware)	N/A	Participation in study has ended	N/A	Promptly	Product Complaint form	N/A

Abbreviations: AE = adverse event; CRF = case report form; eCRF = electronic case report form; ICF = informed consent form; PC = product complaint; SAE = serious adverse event.

*Serious adverse events (including death) caused by disease progression or otherwise due to study disease should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male z ’≤’ z (–.● z○{. z ..(” (•.≤ ●..(.:‘: z (”’○.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 z … (.:‘: z ≤ 8The 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 regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant s pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring z (A; (...× (“… z ’ z◊(z“.3(’ (z○ z (≤ ’≥…≥((•.(z (l RV(z ≥(will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

Prior to continuation of study intervention following pregnancy, the following must occur:

The Sponsor and the relevant IRB/IEC give written approval.

The participant gives signed informed consent.

The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.3.3. Events or Outcomes

Not applicable.

8.3.4. Adverse Events of Special Interest

Adverse events of special interest for abemaciclib include

neutropenia

infections

diarrhea

hepatic events, including increases in AST/ALT

VTEs, and

ILD/pneumonitis.

No AEs need to be adjudicated.

Section 6.8.1 describes supportive care measures for each abemaciclib AESI. Sections 6.5.1.1 and 6.5.1.2 present the dose-modification guidelines for abemaciclib AESIs.

Contact the Sponsor CRP/CRS if questions arise concerning AESIs.

8.4. Pharmacokinetics

Pharmacokinetic samples will be collected from study participants at the visits and times specified in the SoA (Section 1.3.2). At all PK timepoints, a volumetric absorptive microsampling device will be used to collect a blood sample by capillary puncture. In addition, on Cycle 1 Day 1 and Cycle 3 Day 1, a PK sample will also be collected at approximately the same time (within [+/-] 10 minutes) as the blood microsample via venous puncture collection into a vacutainer. It is important to collect accurate information for the time and date of each PK sample on the lab requisition form.

It is also important to collection accurate information for the time and date of doses of blinded study drug around the PK sampling collection times. Accordingly, during the PK sampling period (Cycle 1 Day 1 to Cycle 3 Day 1), participants will complete a paper Patient Dosing Diary

to record the time and date of blinded study drug doses, which will be utilized in PK assessments. The information in this diary should be collected and reviewed on Day 1 of Cycle 2 and Cycle 3 for each prior cycle and be documented in the eCRF. This paper diary is not intended to monitor compliance.

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

Pharmacokinetic samples may be retained for a maximum of 1 year following last 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. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A germline DNA sample that can be used for genetic research will originate from the whole-blood sample collected in Section 8.7.3 for biomarker research. CCI

[redacted]

Genetic samples may be assessed by various methods CCI

[redacted] Regardless of the technology utilized, data generated will be used only for the specific genetic research scope described in this section, and within the limits of this protocol.

Genetic research may lead to the identification of genetic incidental findings. Genetic incidental findings are variations present in germline DNA that are discovered unintentionally and that may nonetheless be of medical value or utility to the physician and the patient. The methods used in

this study to perform genetic research are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, subject to local regulations, no incidental findings will be reported to the patients participating in genetic research.

Genetic samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the study site personnel. Samples will be retained for a maximum of 7 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of study treatment becomes commercially available. Technologies are expected to improve during the 7-year storage period and, therefore, cannot be specifically named. Regardless of the technology utilized, data generated will be used only for the specific genetic research scope described in this section, and within the limits of this protocol.

8.7. Biomarkers

This study will analyze biomarkers relevant to study intervention, mechanism of action, the variable response to study drug(s) (including evaluation of AEs or differences in efficacy), cell cycle, immune function, or pathways associated with breast cancer. Samples collected will enable examination of these questions through the measurement of biomolecules, including DNA, RNA, proteins, lipids, and other circulating or cellular elements. Except for the cases detailed in Sections 8.7.1 (ctDNA sequencing without patient-matched germline subtraction) and 8.7.2 (tumor DNA sequencing without patient-matched germline subtraction), biomarker analyses will not produce interpretable results on germline DNA and therefore will not lead to the identification of genetic incidental findings as described in Section 8.6. Biomarker analyses using DNA as a substrate will generate interpretable information on tumor somatic variants, tumor somatic copy number changes and tumor somatic rearrangements. Biomarker analyses using RNA as substrate will avoid the identification of genetic variants and will focus on quantifying gene expression and reporting tumor somatic gene fusions and other tumor somatic rearrangements. Biomarker analysis results may occur after the CSR is written and therefore a separate biomarker Data Analysis Plan will be developed.

Biomarker samples will include CCI Samples for biomarker research will be collected from all participants as specified in the SoA (Section 1.3), where local regulations allow. It is possible that biomarker data for participants in the study have already been generated from samples that were collected and analyzed prior to enrolling in this

trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.7.1 and 8.7.2.

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

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Sponsor.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the study site personnel. Samples will be retained for a maximum of 7 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of study treatment or after study treatment becomes commercially available. Technologies are expected to improve during the 7-year storage period, and therefore, cannot be specifically named. Regardless of the technology utilized, data generated will be used only for the specific biomarker research scope described in this section, and within the limits of this protocol.

8.7.1. CCI Samples for Biomarker Research

CCI samples for biomarker research will be collected from all participants as specified in the SoA (Section 1.3) where local regulations allow.

CCI

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

CCI analysis may also be performed without germline DNA subtraction. In this case, it may be considered genetic research and the identification of genetic incidental findings is possible. Regardless of whether patient-matched germline DNA subtraction is used or not during the

CCI analysis, the methods used in this study for biomarker analyses are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, no incidental findings will be reported to the patients participating in biomarker research, subject to local regulations.

8.7.2. Tissue Samples for Biomarker Research

Submission of an archival tumor specimen is required, if tissue is available, subject to local regulations. Formalin-fixed paraffin-embedded tissue, if available, should be provided as a block (preferred) or freshly cut unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided.

A biopsy at baseline, as well as at the time of disease progression, is requested, if clinically feasible, per investigator's discretion and subject to participant's consent. Biopsy of a progressing metastatic lesion is preferred whenever possible. Bone biopsies are not preferred but are acceptable.

Pathology report accompanying tumor tissue will be requested. Pathology reports must be coded with the participant number. Personal identifiers, including the participant's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned. Sponsor has a right to retain a portion of the submitted tissue, and archival blocks may be returned to the study site, upon request. Tissue blocks from biopsies collected at baseline/disease progression may be returned to sites if there is available tissue left over, upon request.

Various non-genetic biomarkers with potential prognostic or predictive value for the treatment of breast cancer with study treatment are currently under investigation and may be assessed in this study. CCI

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

germline DNA, is not considered genetic research, and therefore, will not lead to the identification of genetic incidental findings as described in Section 8.6.

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

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

8.7.3. Whole-Blood Sample for Biomarker Research

A whole-blood sample for biomarker research will be collected from all participants as specified in the SoA (Section 1.3), where local regulations allow. CCI [redacted]

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

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics and Medical Resource Utilization

Patient-reported questionnaires will be administered using a provisioned electronic patient-reported outcome (ePRO) device in countries where the questionnaires have been translated into the native language and linguistically validated. Only patients that are literate in an available translation will complete the questionnaires. Questionnaires will be administered on the device in the order presented below. The device will use an alarm feature to remind the patient to complete their questionnaire if the patient has not yet completed their questionnaire on the day it is scheduled. This will be detailed in the eCOA operations manual. In the event that a device does not work properly, the site will follow the mitigation plan specified in the eCOA operations manual for collecting this data.

Patient-reported outcomes (PRO) will be used to compare changes in cancer-related symptoms, physical function, adverse effect of diarrhea, and other health-related quality of life (HRQoL) outcomes between treatment arms. Data from the EQ-5D-5L will be used to generate health utility data by treatment arm. See Section 1.3.1 for PRO SoA.

Patients will receive the ePRO device at C1D1. All baseline assessment PRO questionnaires will be administered electronically on C1D1 prior to extensive interaction with site staff and study drug administration. “Worst pain” as a single item is an exception and not administered at C1D1 baseline since it is also part of the mBPI-SF scale. EORTC IL-19 is also an exception and not

administered at baseline due to overlapping questions with EORTC QLQ-C30. Subsequent assessments, apart from the SFU visit, will be completed at home according to the SoA (Section 1.3.1) to minimize required activities during clinic visits. At the SFU visit, patients will complete the specified assessments on the patient's ePRO device on site; therefore, patients will be asked to bring their device with them this SFU visit.

Estimated completion time is 5-8 minutes for the PRO items collected on a monthly schedule.

8.9.1. Worst Pain NRS Item Extracted from the BPI-SF

The patient-reported mBPI-SF "Worst Pain Single Item" is a single-item, 11-point numeric rating scale (NRS) scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine." This "Worst Pain Single Item" is also included in the mBPI-SF 11-item scale described in Section 8.9.2, and patients will complete either the single item or the scale, but not both on the same day. CCI [redacted] sites will not administer this instrument. The CCI assessments for mBPI-SF "Worst Pain Single Item" will be collected during the study period as described in Section 1.3.1.

8.9.2. Modified BPI-SF Scale

The mBPI-SF (Cleeland 1991) is an 11-item instrument used as a multiple-item measure of pain intensity and its impact on daily function (i.e., pain interference). In addition to pain intensity (4 items: "worst pain", "least pain", "average pain", "pain now"), the mBPI-SF is designed for patients to record pain interference with function (7 pain interference items: general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, and enjoyment of life). Responses for the mBPI-SF items are captured through the use of 11-point NRS anchored at 0 (no pain or does not interfere) and range through 10 (pain as bad as you can imagine or completely interferes). CCI [redacted]

8.9.3. PRO-CTCAE-Diarrhea

The PRO-CTCAE is a measurement system developed by the National Cancer Institute to collect symptomatic AE data from patients with cancer enrolled in clinical trials (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE item library (Version 1.0) includes 78 symptomatic AE and a total of 124 items; some AEs include multiple items (e.g., frequency (F), severity (S), interference (I), and presence/absence (P) [NCI 2017). These items were developed to assess symptomatic AEs from the patient perspective and complement the CTCAE data collected at the site level (Basch et al. 2014; Atkinson et al. 2016).

A single question from the PRO-CTCAE item library was selected to characterize diarrhea (F). [redacted]

8.9.4. EORTC QLQ-C30

Health-related quality of life will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30; Aaronson et al. 1993). Broadly used in cancer trials and available in over 80 different languages,

EORTC QLQ-C30 is a reliable and validated tool that has supported quality-of-life claims in both Food and Drug Administration and European Medicines Evaluation Agency labels.

The full EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covering 3 dimensions regarding the patient's experience during the past week:

- global health status/quality of life (2 items)
- functional scales – 15 total items addressing either physical (described in EORTC IL-19 below), role (limited in daily activities, limited in hobbies or leisure), emotional (feel tense, worry, irritable, depressed), cognitive (concentrating, remembering), or social functioning (interference with family life, interference with social activities), and
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact).

Patients select one of four response options for each EORTC functional and symptom item: "Not at All", "A little", "Quite a bit" and "Very much". EORTC global health status and quality of life items include seven numeric response options: 1 ("Very poor") up to 7 ("Excellent").

Beginning C1D1, patients will complete the EORTC QLQ-C30 assessment using the ePRO device CCI [redacted]

8.9.5. EORTC IL-19

The EORTC IL-19 consists of 5 items that are identical to the EORTC QLQ-C30 physical functioning scale (Items 1-5: trouble with "doing strenuous activities", "taking a long walk", "taking a short walk"; "need to stay in bed or chair most of the day", "need help eating, dressing, washing, using the toilet"). This assessment will be completed by patients at home on an ePRO device on an CCI [redacted] schedule as described in Section 1.3.1. To minimize patient burden, the CCI [redacted]

8.9.6. EQ-5D-5L

Health status will be assessed using the EQ-5D-5L (Pickard et al. 2007; Janssen et al. 2008; Herdman et al. 2011). These utility measures are an important input for economic evaluations by global health technology assessment organizations that examine the value of treatment interventions. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and 5-level (no problem, slight, moderate, severe, or extreme problem) assessment. Additionally, patients will indicate their current health status by marking on a visual analog scale ranging from 100 (best health you can imagine) to 0 (worst health you can imagine). The EQ-5D-5L is designed for self-completion by respondents, is cognitively simple, takes only a few minutes to complete, with a recall period of "today," and will be completed by patient using an electronic device, CCI [redacted] according to described in Section 1.3.1.

8.9.7. Health Care Resource Utilization

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization (HCRU) associated with medical encounters and analgesic use.

The data collected in the CRF, starting at C1D1, up to and including SFU will

include the reasons and duration of hospitalizations and emergency room visits, and include analgesic use.

The Sponsor may use the collected data to conduct economic analyses.

9. Statistical Considerations

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

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 statistical analysis plan (SAP) and the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to first visit when a participant receives study drug or any other protocol intervention and will include a more technical and detailed description of the statistical analyses described in this section.

9.1. Statistical Hypotheses

Primary Hypothesis (Arm A versus Arm B): Treatment of participants with advanced/metastatic HR+, HER2- breast cancer with abemaciclib in combination with fulvestrant after prior treatment with CDK4 & 6 inhibitor-based regimen will provide a clinically meaningful increase in PFS over treatment with fulvestrant in combination with placebo.

9.1.1. Multiplicity Adjustment

CCI

9.2. Analyses Sets

The populations for analysis are defined as follows.

Population	Description
Entered	All participants who sign the ICF
ITT	All participants randomly assigned to study treatment, regardless of whether they take any doses of study treatment, or if they take the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned
Safety	All participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the study treatment they actually received
PK	All participants who have received at least 1 dose of abemaciclib, have at least 1 evaluable PK sample, and have sufficient dosing information

Abbreviations: ICF = informed consent form; ITT = intention to treat; PK = pharmacokinetics.

9.3. Statistical Analyses

9.3.1. General Considerations

Participants will be randomized using the following stratification factors:

- Geography (3 levels)
  [redacted]
- Presence of visceral metastases (2 levels)
  - Yes, or
  - No
- Duration on prior adjuvant/metastatic CDK4 & 6 inhibitor-based regimen (2 levels):
  [redacted]

[redacted]

Any modifications or clarifications to the data analysis methods will be described and justified in the SAP before unblinding.

The primary analysis of the primary endpoint of PFS is event driven and will be performed when the required number of PFS events has been observed (for interim and final analyses). See Sections 9.4.2 and 9.5. 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.

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

9.3.1.1. Treatment Group Considerations

9.3.1.1.1. Participant disposition

A detailed description of participant disposition will be provided, according to CONSORT publishing requirements, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated, as well as number and percentage of participants completing the study, as defined in the SAP, or discontinuing prior to study completion (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.3.1.1.2. Participant characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target participant population considered for regulatory approval.

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

Other participant baseline characteristics will be summarized by treatment arm as deemed appropriate.

9.3.1.1.3. Concomitant therapy

A summary of prior and concomitant medications by treatment will be reported.

9.3.1.1.4. Treatment compliance

Study treatment compliance will be assessed as the proportion of treatment that is actually taken relative to what is expected, after accounting for protocol-defined dose adjustments. For oral components of study treatment, study treatment taken will be derived from the difference between the total number of pills dispensed and returned over the course of the participant's treatment.

9.3.1.1.5. Extent of exposure

The duration on therapy, dose omissions, dose reductions, dose delays, and dose intensity for each drug will be summarized for all treated participants by treatment arm.

9.3.1.1.6. Post-discontinuation treatment therapy

The numbers and percentages of participants receiving post-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. Post-study treatment therapy will be summarized by treatment arm.

9.3.2. Primary Endpoint/Estimand Analysis

The primary endpoint, PFS by investigator assessment, is defined as the time from randomization until the first occurrence of documented disease progression as determined by investigator assessment per RECIST 1.1, or death from any cause in the absence of documented progressive disease. Participants known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment (a detailed PFS event/censoring scheme will be provided in the SAP). PFS will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata in the ITT population. The corresponding hazard ratio between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. PFS curves, median PFS, and PFS rates at various time points with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for PFS will be described in the SAP.

CCI [redacted]

9.3.3. Secondary Endpoint(s) Analysis

9.3.3.1. Progression-Free Survival by Blinded Independent Central Review (PFS by BICR)

A PFS analysis based on blinded independent central review data will be conducted. Details can be found in the Central Review SAP.

9.3.3.2. Objective Response Rate (ORR), Disease Control Rate (DCR), Clinical Benefit Rate (CBR)

Objective response rate (ORR) is defined as the number of participants who achieve a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the total number of participants randomized to the corresponding treatment arm. Confirmation of CR and PR is not required.

Disease control rate (DCR) is defined as the number of participants who achieve a BOR of CR, PR, or SD divided by the total number of participants randomized to the corresponding treatment arm (ITT population). Confirmation of CR and PR is not required.

Clinical benefit rate (CBR) is defined as the number of participants who achieved a BOR of CR (i k 6((l U(E(● ”, divided by the total number of participants randomized to the corresponding treatment arm (ITT population). Confirmation of CR and PR is not required.

For each of these rates, point estimates and 95% confidence intervals (using the normal approximation to the binomial) will be calculated by treatment arm. Stratified tests comparing these rates between treatment arms will be conducted using the Cochran-Mantel-Haenszel test adjusting for the randomization strata.

9.3.3.3. Duration of Response (DoR)

Duration of response (DoR) is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented disease progression or recurrence.

9.3.3.4. Overall Survival (OS)

Overall survival (OS) is an important secondary endpoint for this study and is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Further details concerning OS analyses can be found in the SAP.

9.3.3.5. Health Outcomes

Time to sustained worsening of worst pain is defined from the randomization to the time of the –’ (’ ≤ . z . .(2 A(’ 3(’ (”.(. ...×○(z ..z“.(.–(”.(. (z’ (≤ .(. ’”(≤ –’ ● z ’ (’ (”.(. next consecutive week. Time to worsening of worst pain will be summarized for each arm by the Kaplan-Meier method and will be compared between the arms using the stratified log-rank test.

Time to worsening of physical function is defined as the time from randomization to the first <;-point decrease from baseline with confirmation at the next cycle. Time to worsening of

physical function will be summarized for each arm by the Kaplan-Meier method, and the stratified log-rank test will be used to compare between the 2 arms.

For each participant with data from baseline and at least 1 post-baseline visit, the change from baseline at each time point, and maximum change from baseline score will be calculated for each scale of each instrument. The reason and number of missing and incomplete questionnaires and/or assessments by visit will be summarized for each instrument and arm.

HCRU frequency counts of hospitalizations, emergency room visits, and analgesic use will be summarized descriptively for each arm.

Full censoring rules for these endpoints will be described in the SAP. Further analysis details will be described in the SAP.

9.3.4. Safety Analyses

All participants in the safety analysis set in Section 9.3 [illegible]

The most current version of the Medical Dictionary for Regulatory Activities (MedDRA®) will [illegible] be used in the treatment-[illegible]-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) [illegible]

Safety analyses will include [illegible]

[illegible]
[illegible]
[illegible]
discontinuations from study treatment [illegible]
treatment-[illegible]
treatment-emergent abnormal changes in vital signs and ECGs

The number of participants with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of participants with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

Preexisting conditions are defined as AEs that are either ongoing or end on or after informed consent.

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

9.3.5. Other 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.

9.3.5.1. Exploratory Analyses

9.3.5.2. Pharmacokinetic and Exposure-Response Analyses

Pharmacokinetic analyses will be conducted on all patients who have received

- at least 1 dose of abemaciclib
- at least 1 evaluable PK sample, and
- sufficient dosing information.

Observed concentration data for each analyte will be graphically assessed and may also be summarized by time and/or dose.

Population PK modeling approaches may also be used to compute mean PK parameters (for example, clearance, exposure, volume of distribution) and interindividual PK variability.

9.4. Interim Analysis

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

Unblinding details are specified in a separate blinding and unblinding plan document.

9.4.1. Safety Interim Analyses

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

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

There will be no prespecified rules for stopping the trial due to safety concerns.

The DMC will meet and review the overall data approximately every 6 months thereafter while patients remain in the on-study intervention periods. At the recommendation of the DMC, the frequency of safety interim analyses may be modified. See Section 10.1.5 for further details.

9.4.2. Efficacy/Futility Interim Analyses

CCI

Analysis	Number of Events	Information Fraction	HR boundary for Futility	Critical One-Sided P-value Boundary for Efficacy	Cumulative Type I Error Rate	Cumulative Power under Assumed HR of 0.7
Interim PFS	CCI	CCI	CCI	CCI	CCI	CCI
Final PFS	CCI	CCI	CCI	CCI	CCI	CCI

Abbreviations: HR = hazard ratio; PFS = progression-free survival.

9.5. Sample Size Determination

The study will randomize approximately 350 participants in 1:1 randomization ratio, with approximately 175 participants per treatment arm.

CCI

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

Applicable ICH Good Clinical Practice (GCP) Guidelines

Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant 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 to protect the z ’≤ z (personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the Sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the z ’≤ z (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. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor (≤… …(z .(≤ ● ♂z (’ ”(local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

10.1.5.2. Early Safety Data Review

Participant safety will be continuously monitored by the external data monitoring committee, which includes safety signal detection at any time during the study.

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

10.1.6. Dissemination of Clinical Study Data

Reports

The Sponsor will disclose a summary of study information, including tabular study results, on publicly available websites ”…..(…. ’ .≥(• (○ ≤z◊(◊z ((.:“ ◊z ’ 8 The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The Sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pha ● z≤ × ’ …’≤((“……’≤(≥z z8(Uz z(z .(z z’◊• ◦(. (request 6 months after the indication studied has been approved in the US and EU and after

’● z (• ♂≤z ’ (z≤≤.. z ≤.ﬁ(”’≤”…..(’ (♎z ..8(g (… ’ z ’ (≥z .(. –(≥z z(… … (’ (
currently set once dz z(z .(● z≥.(z z’♎• ♌8

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data- ”z ’ “(z“ …● … 8(Uz z(z ≥(documents, including the study protocol, SAP, CSR, blank or annotated CRFs will be provided in a secure data- ”z ’ “(… ’ ● … (– (((A(.z (..(z♎8

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

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This might include laboratory tests, medical records, and clinical notes.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study, and important excursions from the QTLs and remedial actions taken will be summarized in the CSR.

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (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 (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

An 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). 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(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in ”.(≤… z◊ …≥ (≥z z• z .(. .●, and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the ’ …”“z (’.8

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.

Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

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

Study or Site Termination

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

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

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

For study termination:

Discontinuation of further study intervention development

For site termination:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor s procedures, or GCP guidelines

Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator

Total number of participants included earlier than expected.

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

10.1.10. Publication Policy

In accordance with the S (• ♂≤z ’ (♂≤ , the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

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

10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of abemaciclib.

Sample Type	Custodian	Retention Period after Last Patient Visit*
Long-term storage samples	Sponsor or Designee	CCI
Biomarkers	Sponsor or Designee	CCI
Pharmacokinetics	Sponsor or Designee	CCI
Genetics	Sponsor or Designee	CCI

*Retention periods may differ locally. See Appendix 7, Section 10.7 for country-specific differences from the above.

The Sponsor has a right to retain a portion of submitted biopsy tissue. Archival blocks may be returned to the study site, upon request. Tissue blocks from biopsies collected at baseline/disease progression may be returned to sites if there is available tissue left over, upon request.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory or by the local laboratory as indicated.

Local laboratory results are only required if 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 obtained at the same time.

- Discrepancies between local and central laboratory results that may impact eligibility or treatment decisions will not be considered protocol deviations.
- If the local laboratory results are used to make either a study intervention decision or response evaluation, the local results must be recorded.
- If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, increased blood pressure, neutrophils decreased, etc.) and it is known to be related to an existing diagnosis (for example, hypertension, neutropenia, etc.) this should be reported in the CRF as an AE. Do not enter the test abnormality; enter the disease, diagnosis, or categorical term.

In circumstances where the Sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for participant inclusion and exclusion are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Sponsor-designated laboratory
Hemoglobin	
Hematocrit	
Leukocytes (WBC)	
Neutrophils absolute	
Lymphocytes absolute	
Platelets	
Clinical Chemistry	Assayed by Sponsor-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN) or blood urea	
Creatinine	
Total protein	
Albumin	
Calcium	
Phosphate	
Glucose	
Coagulation	
Prothrombin time, INR (PT-INR)	Evaluated by local laboratory
Hormones (Female)	
Serum pregnancy test	Evaluated by local laboratory
Urine pregnancy test	Evaluated by local laboratory
Follicle-stimulating hormone (FSH)	Evaluated by local laboratory Performed as needed to confirm postmenopausal status
Other Testing	
Cystatin C	Assayed by Sponsor-designated laboratory Obtained as clinically indicated
Abemaciclib Pharmacokinetic Samples LSN3106726 (M20)	Assayed by Sponsor-designated laboratory. Results will not be provided to the investigative sites

Clinical Laboratory Tests	Comments
LSN2839567 (M2)	
Genetics & Biomarker Samples CCI CCI CCI CCI CCI	CCI CCI
Additional Hepatic Monitoring	See Section 10.5, Appendix 5.

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the ’ …’“z ((• .(• .(……..(.”z (… .≤ .≥(– (”.(. z ’≤’ z (≤ ≥’ ’ 8

The disease/disorder being studied or expected progression, signs, or symptoms of the [illegible] condition.

Events, including death, caused by disease progression or otherwise due to study disease should not be reported unless the investigator deems them to be possibly related to study treatment.

Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or [illegible] 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

[illegible] life functions.

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

e. Is a congenital anomaly/birth defect

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

f. Other situations:

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should 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. Definition of Product Complaints

Product Complaint

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

- Deficiencies in labeling information, and
- Use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.

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

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

AE, SAE, and Product Complaint Recording

When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/product complaint information in

practice. AE/SAE information is reported on the appropriate (e)CRF page and product complaint information is reported on the Product Complaint Form.

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

It is **not** z≤≤… z• ○(– (”.(: …”“z ((…≥(” ≤ ’…(–(”.(. z ’≤’ z (● .≥’≤z○(records to Sponsor or designee in lieu of completion of the (e)CRF page for AE/SAE and the Product Complaint Form for product complaints.

There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to assign AE severity grades.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship/

A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consu○(”.(b …”“z (S ≤” .(2bS3(z ≥: (i ≥ ≤(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 an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

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

SAE Reporting via Paper Form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.
Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
Contacts for SAE reporting can be found in the SAE form.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward 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 evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The Sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the b … ”“z (S ≤’ .(and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of child bearing potential	Females are considered a woman of child bearing potential if they have had at least one cycle of menses, or they have Tanner 4 breast development Any amount of spotting should be considered menarche. If Tanner Staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.
Women not of child bearing potential	Females are considered women not of child bearing potential if they have a congenital anomaly such as Mullerian agenesis resulting in confirmed infertility, they are infertile due to surgical sterilization, or they are post-menopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy
Post-menopausal state	The post-menopausal state is defined as: 1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND With a follicle-stimulating hormone 40 mIU/mL; or 3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy *Women should not be taking medications during amenorrhea such as oral contraceptives, hormone replacement therapy (HRT)s, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Please see guidance for specific patient populations below:

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle

	1
agree to either remain abstinent, or stay in a same-sex relationship without sexual relationships with males, and not plan a pregnancy during the study	use periodic abstinence methods o calendar o ovulation o symptothermal, or o post-ovulation declare abstinence just for the duration of a trial or use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle

Topic	Explanation
Pregnancy testing	Negative serum result at screening followed by a negative urine result within 48 hours prior to first treatment exposure
	Note: subsequent pregnancy testing is compound specific
Contraception	Should use highly effective contraception (less than 1% failure rate) to prevent pregnancy while receiving study treatment and for 3 weeks after the last dose of blinded study drug and for 2 years after the last dose of fulvestrant (or according to local approved fulvestrant label)

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception	fallopian tube sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please refer to WNOCBP definition above. total abstinence

	vasectomy, if only sexual partner fallopian tube implants, if confirmed by hysterosalpingogram intrauterine devices (only hormone free)
Effective contraception	male or female condoms with spermicide diaphragms with spermicide or cervical sponges barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide. Note: Male and female condoms should not be used in combination.
Ineffective forms of contraception	spermicide alone periodic abstinence fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) withdrawal post coital douche lactational amenorrhea

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

Hepatic Evaluation Testing

See Section 10.2, Appendix 2 for guidance on appropriate test selection.

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

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

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

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

HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

a Not required if anti-actin antibody is tested.

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

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

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

10.6. Appendix 6: Inducers and Strong Inhibitors of CYP3A

Strong Inducers of CYP3A
Aminoglutethimide
Apalutamide
Carbamazepine
Enzalutamide
Fosphenytoin (see also phenytoin)
Ivosidenib
Lumacaftor
Mitotane
Phenobarbital/phenobarbitone
Phenytoin
Rifabutin
Rifampicin (rifampin)
Rifapentine
l (c ” (

Moderate Inducers of CYP3A
Bosentan
Cenobamate
Dabrafenib
Danshen (*Salvia miltiorrhiza*)
Efavirenz
Elagolix
Encorafenib
Etravirine
Genistein
Lopinavir (alone)
Lorlatinib
Modafinil
Nafcillin (intravenous)
Pentobarbital
Primidone
Thioridazine
Tipranavir and ritonavir
Tocilizumab (atlizumab)

Strong Inhibitors of CYP3A
Atazanavir and cobicistat
Boceprevir
Ceritinib
Clarithromycin
Cobicistat (see atazanavir and cobicistat)
Conivaptan
Danoprevir and ritonavir
Elvitegravir and ritonavir
Fosamprenavir and ritonavir

Grapefruit juice
Idelalisib
Indinavir and ritonavir
Itraconazole
Josamycin
Ketoconazole
Lonafarnib
Lopinavir and ritonavir
Mifepristone
Nefazodone
Nelfinavir
Posaconazole
Ribociclib
Ritonavir
Saquinavir and ritonavir
Telithromycin
Tipranavir and ritonavir
Tucatinib
Viekira Pak, Viekira XR (paritaprevir and ritonavir and ombitasvir and/or dasabuvir)
Voriconazole

10.7. Appendix 7: Country-Specific Requirements

10.7.1. Discontinuation of Inadvertently Enrolled Participants in the United Kingdom

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

10.7.2. Removal of the Legally Authorized Representative, Legal Guardian, Parents, Designee, Surrogate, and Caregiver in Germany

The informed consent process (Section 10.1.3), reporting of adverse events (Section 8.3), and request to discontinue/withdraw from the study (Section 7.2) must be completed by the study participant; it is not permitted in Germany for these activities to be conducted by the z ’≤’ z (z … 6(≥…“ …6(≤z .:’ ..6(“z .6((○:z∞ (z ” ized representative.

10.8. Appendix 8: Provisions for Changes in Study Conduct during Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the S (’ …(z oval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

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

Considerations for making a change

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

Informed consent

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

z ’≤’ z ’ (’ (.● .(. ’ ’ 6(z (≥.-’ .≥(’ (l .≤’ (k .● .(o ’ ’ 6

alternate delivery of study intervention and ancillary supplies, and

provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

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

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of Remote Visits

Telemedicine:
Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.

Mobile healthcare:
Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the Sponsor. Procedures performed at such visits may include, but are not limited to, concomitant medications, collection of blood samples, physical assessments, administration of PROs if validated for these types of visits, administration of study intervention, and collection of health information.

Other alternative locations:
Other procedures may be done at an alternate location in exceptional circumstances.

Data Capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety Reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged.

Return to On-site Visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for tests outlined in the Clinical Laboratory Tests appendix (Appendix 2, Section 10.2). The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the Sponsor to determine appropriate actions. These actions may include

asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit

z ×’ “(”.(. z ’≤ z (≥…“ …(. (“ ((”.(.’ .(z ≥(.≤.’. .(. ≥ (♂…((z(z ’≤ z (• .’.’z⟜

arranging delivery of study supplies, and

working with the Sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location, such as an infusion center.

These requirements must be met before action is taken:

Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including

When delivering supplies to a location other than the study site (for example,

Sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).

Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirements must be met:

Only authorized study personnel may supply, prepare, or administer study intervention.

Screening period guidance

The screening procedures per the usual SoA should be followed

Adjustments to visit windows

should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the Sponsor. This minimizes missing data and preserves the intended conduct of the study.

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

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the source documentation and should be transferred to the site in a secure and timely manner.

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
authorized IMP	*Applicable to the EU only:* a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product
BID	twice a day, at least approximately 6 hours apart
BOR	best overall response
BPI-SF	Brief Pain Inventory-short form
blinding	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the Sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CDK4 & 6	cyclin-dependent kinases 4 and 6
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials

CNS	central nervous system
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CR	complete response
CRF/eCRF	case report form/electronic case report form
CRP/CRS	clinical research physician or clinical research scientist: 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.
CSR	clinical study report
CT	computed tomography
CCI	[redacted]
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D. Bil	direct bilirubin
Device deficiencies	Equivalent to product complaint
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DNA	deoxyribonucleic acid
DRFS	distant relapse free survival
eCOA	electronic Clinical Outcome Assessment
ECOG PS	Eastern Cooperative Oncology Group performance status
ECG	electrocardiogram
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 QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQOL 5 Dimension 5 Level
ER	estrogen receptor
ERB	ethical review board
ERCP	endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
Estimand	Describes the quantity (population parameter) to be estimated to characterize a causal treatment effect to address a specific study objective
ET	endocrine therapy
FSH	follicle-stimulating hormone
GCP	good clinical practice
GDPR	EU General Data Protection Regulation
GGT	gamma-glutamyltransferase
HCRU	Health Care Resource Utilization
HDV	hepatitis D virus
HR+	hormone receptor positive
HER2-	human epidermal growth factor receptor-2 negative
HER2	human epidermal growth factor receptor-2
HIV	human immunodeficiency virus
HR	hormone receptor
HRQoL	health-related quality of life
IB	b … ”“z (S ≤” …
ICF	informed consent form
ICH	International Council for Harmonisation
IDFS	invasive disease-free survival
IEC	independent ethics committees
IHC	immunohistochemistry

ILD	interstitial lung disease
IMP	b …”“z ’ z◁f .≧’≦ z◁i ≥ ≤(2 …(z○ (’ …”“z ’ z◁(≥ ≤ 3 A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study ”z (z .(…○..z ((”.(. z ’≦’ z (≥.≦’ ((z ’≦’ z .8(b – ● .≧(≤ … (’ (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
IRC	Internal Review Committee
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant assigned to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
MBC	metastatic breast cancer
mBPI-SF	modified Brief Pain Inventory - short form
MedDRA	Medical Dictionary for Regulatory Activities

medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling, for example, Summary of Product Characteristics, IB, local label, protocol, or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NRS	numeric rating scale
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 Throughout this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational intervention or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials
PC	product complaint
PFS	progression-free survival
CCI	[redacted]
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
PR	partial response
PRO	patient-reported outcomes
PET-CT	Positron emission tomography-computed tomography
RECIST	Response Evaluation Criteria in Solid Tumors
SAC	Statistical Analysis Centre
SAE	serious adverse event
SAP	statistical analysis plan

screen	The act of determining if an individual meets the minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SERD	select estrogen receptor degrader
SFU	short-term follow-up
SMD	senior management designee
SoA	Schedule of Activities
SRE	skeletal-related event
SUSAR	Suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
UK	United Kingdom
US	United States
V	visit
VTE	venous thromboembolic event
WOCBP	women of child-bearing potential

10.10. Appendix 10: Protocol Amendment History

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

Amendment [c]: (17-Feb 2022)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall Rationale for the Amendment:

The main rationale for the current amendment is to incorporate feedback from the FDA.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.1.2 Re-escalation Criteria for Blinded Study Drug	Updated text to indicate that re-escalation to the prior dose will be permitted only once for the blinded study drug	FDA feedback
Section 6.8.2 Bisphosphonates and RANK-L Targeted Agents	Added text regarding concomitant therapy with bisphosphonates and RANK-L targeted agents	For clarity
Section 9.4.2 Efficacy/Futility Interim Analyses	Added futility stopping rule and detailed the process of the futility interim analysis	FDA feedback
Section 10.4. Appendix 4: Contraceptive and Barrier Guidance	Updated examples of highly effective contraception	For clarity
Throughout the protocol	Minor editorial and formatting changes	Correction

Amendment [b]: (09-Dec-2021)

Overall Rationale for the Amendment:

The main rationale for the current amendment is to incorporate feedback from the Voluntary Harmonisation Procedure Clinical Trial Application.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Added clarification regarding the duration of study period.	Voluntary Harmonisation Procedure Clinical Trial Application (VHP CTA) feedback
	Added coagulation tests at baseline and as clinically indicated for liver toxicity.	
	Removed 14-day visit interval tolerance at study period III.	Clarification regarding study periods
	Updated text to clarify the time points at which the participant should return study drugs.	Clarification
Section 5.1 Inclusion Criteria	Updated Inclusion Criterion 11b related to contraception duration for women of childbearing potential (WOBCP) using fulvestrant.	VHP CTA feedback
	Added clarification regarding WOBCP who are completely abstinent or in same-sex relationships.	Clarification
Section 5.2 Exclusion Criteria	Added numbering that was missing for Criterion 19.	Correction
Section 6.1.2 General Dosing Instructions	Clarified that the participant can be started at a lower dose if determined by the investigator.	Clarification
Section 6.3.1 Emergency Unblinding	Added a description of unblinding of study medication in emergency situations.	VHP CTA feedback
Section 6.3.2 Inadvertent Unblinding	Added text regarding inadvertent unblinding.	
Section 6.6 Continued Access to Study Intervention after the End of the Study	Added clarification about continued access to study treatment and that placebo will no longer be administered during the continued access period.	VHP CTA feedback

Section # and Name	Description of Change	Brief Rationale
Section 8.7.2 Tissue Samples for Biomarker Research	Updated text to clarify that biopsies are requested only if clinically feasible.	VHP CTA feedback
Section 9.3.2 Primary Endpoint/Estimand Analysis	Added text that primary endpoint analyses will be done in the ITT population.	VHP CTA feedback
Section 9.3.3.4 Overall Survival (OS)	Updated definition of overall survival.	Clarification
Section 9.4.2 Efficacy Interim Analyses	Updated the text for efficacy interim analysis.	VHP CTA feedback
	Added clarification that the trial will not stop early to conclude efficacy based on the interim analysis of efficacy.	
Section 10.1.6 Dissemination of Clinical Study Data	Added clarification that trial results will be posted in EudraCT.	VHP CTA feedback
Appendix 2 Clinical Laboratory Tests	Added PT and INR as coagulation tests.	VHP CTA feedback
Throughout the Protocol	Minor formatting and editorial changes.	Correction

Amendment [a]: (02-Sep-2021)

This amendment occurred before the protocol was submitted to any EU member state.

Overall Rationale for the Amendment:

The overall rationale for the current amendment is to add the biomarker exploratory objective and endpoint that were inadvertently omitted from the original protocol. Additional changes were made and are summarized in the below table; minor typographical or formatting edits are not presented.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (main table)	Line item for Adverse Event Collection/CTCAE Grading Removed note cross-referencing to Section 10.3 (Appendix 3).	For clarity
1.3. Schedule of Activities (main table)	Line item for Radiologic imaging according to RECIST 1.1 Added	For clarity
1.3. Schedule of Activities (main table)	Line item for Bone scintigraphy Added	For clarity
1.3. Schedule of Activities (main table)	Line item for Patient Dosing Diary (paper) from cell and then shaded entire cell across Study Period I.	Error correction and formatting
1.3. Schedule of Activities (main table)	Line item for Patient Dosing Diary (paper) Removed shading from cell across Study Period II.	Formatting
1.3. Schedule of Activities (main table)	Line item for Archival tumor tissue Edited note indicating that archival tumor Archival tumor tissue is now required, if available.	For clarity
1.3. Schedule of Activities (main table)	Line item for Tumor biopsy/biopsies Added note stating biopsy/biopsies are discretion, and cross-reference to protocol section.	For clarity

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (main table)	CCI [redacted]	For clarity
1.3. Continued-Access SoA	Line item for AE collection – Deleted note cross-referencing to Section 10.3 (Appendix 3)	For clarity
2.2.2. CDK4 & 6 Inhibition in HR+, HER2- Breast Cancer	Reworded text at the end of the second paragraph – deleting "second- or third-line therapy" and adding "ET-resistant MBC".	For clarity
2.3.1. Risk Assessment	In the Study Procedures, the fourth paragraph has been edited to indicate the tumor biopsy is requested if feasible, per investigator's discretion.	For clarity
3. Objectives, Endpoints, and Estimands	Added biomarker exploratory objective and endpoint.	Error correction – this content was omitted from original protocol.
5.4. Screen Failures	Reworded rescreening text in second and third paragraphs.	For clarity
6.5.1.1. Blinded Study Drug Dose Adjustments for Treatment-Emergent, Related* Adverse Events	For the ALT/AST Increased line item in the dose adjustments table, ULN format has been replaced with CTCAE grades.	For clarity and consistency
6.5.2. Fulvestrant	Added text stating that fulvestrant dose may be re-escalated at the discretion of the investigator and after consultation with the Sponsor CRP/CRS.	For clarity
8.7.2. Tissue Samples for Biomarker Research	Added text in the first paragraph indicating that archival tumor specimen is "required, if tissue is available, subject to local regulations".	For clarity
8.7.2. Tissue Samples for Biomarker Research	Added text in the second paragraph "A biopsy at baseline, as well as at the time of disease progression, is requested, if feasible, per investigator's discretion."	For clarity

Section # and Name	Description of Change	Brief Rationale
10.1.12. Sample Retention	Text directly below the table has been .≥’ .≥.((z .(.”z (z ≤’’ z◊(• ○ ≤× (● z (• .(…. .≥.((”.(. ≥ (’ .ß((… … 8 R○ (≥.ﻩ..≥.(… (z ’ “(1 ♂≥..(z ≥(tissue samples collected on study will not • .(…. .≥ (z ≥(…ø≤.≥.(’ (’ ”(m’ .(. blocks from biopsies collected at baseline/disease progression may be returned to sites if there is available ’ .(ﻩ.–(..ß((… … 8 (((	For consistency and clarity
10.2. Appendix 2: Clinical Laboratory Tests	In Genetics & Biomarker Samples section of table ≥.ﻩ..≥.(’ z○ (– ● (♂ .(’ ..● ((.z≥ (m ● (’ .(– ● (• ’ :• ’ ’… 8	For clarity
10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints	Assessment of Intensity: Deleted text stating that post-baseline grading of all laboratory values should be done per normal reference limit references, regardless of whether the assessment is normal or abnormal at baseline.	For consistency with CTCAE v5.0

11. References

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376. https://doi.org/10.1093/jnci/85.5.365

Alvarez-Fernandez M, Malumbres M. Mechanisms of Sensitivity and Resistance to CDK4/6 Inhibition. *Cancer Cell*. 2020;37(4):514-529. https://doi.org/10.1016/j.ccell.2020.03.010

André F, Ciruelos E, Rubovszky G, et al. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. https://doi.org/10.1056/NEJMoa1813904

Atkinson TM, Ryan SJ, Bennett AV, et al. The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systemic review. *Support Care Cancer.* 2016;24(8):3669-3676. https://doi.org/10.1007/s00520-016-3297-9

Basch E, Reeve BB, Mitchell SA, et al. [illegible] -reported outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst*. 2014;106(9): dju244. https://doi.org/10.1093/jnci/dju244

Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012a;366(6):520-529. https://doi.org/10.1056/NEJMoa1109653

Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012b, 366(2):109-119. https://doi.org/10.1056/NEJMoa1113216

Buowari OY. Complications of venepuncture. *Advances in Bioscience and Biotechnology*, 2013, 4, 126-128. https://doi.org/10.4236/abb.2013.41A018

Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol.* 2020;31(12):1623 1649. https://doi.org/10.1016/j.annonc.2020.09.010

Cleeland CS. Pain assessment in cancer. In: Osoba D(ed). Effect of Cancer on Quality of Life. Chapter 21. Boca Raton (FL): CRC Press;1991.

Crawford J, Armitage J, Balducci L, et al.; National Comprehensive Cancer Network. Myeloid growth factors. *J Natl Compr Cancer Netw.* 2009;7(1):64-83. https://doi.org/10.6004/jnccn.2009.0006

Cox DR. Regression models and life-tables. *J Royal Stat Soc Ser B*. 1972;34(2):187-220.

Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224. https://doi.org/10.1158/1078-0432.CCR-17-0754

Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US National Cancer b ’ … (i z ’… -Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncol.* 2015;1(8):1051-1059. https://doi.org/10.1001/jamaoncol.2015.2639

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. https://doi.org/10.1016/j.ejca.2008.10.026

Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936. https://doi.org/10.1056/NEJMoa1607303

Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2013;31(6):794-810. https://doi.org/10.1200/JCO.2012.45.8661

Fulvestrant [package insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP; 2010.

Garcia J, Liu SZ, Louie AY. Biological effects of MRI contrast agents: gadolinium retention, potential mechanisms and a role for phosphorus. *Philos Trans A Math Phys Eng Sci*. 2017;375(2107):20170180. https://doi.org/10.1098/rsta.2017.0180

Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646. https://doi.org/10.1200/JCO.2017.75.6155

Gul A, Leyland-Jones B, Dey N, De P. A combination of the PI3K pathway inhibitor plus cell cycle pathway inhibitor to combat endocrine resistance in hormone receptor-positive breast cancer: a genomic algorithm-based treatment approach. *Am J Cancer Res.* 2018;8(12):2359-2376.

Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784-2795. https://doi.org/10.1200/JCO.2009.25.6529

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727 1736. https://doi.org/10.1007/s11136-011-9903-x

Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375(18):1738-1748. https://doi.org/10.1056/NEJMoa1609709

Janssen MF, Birnie E, Haagsma JA, Bonsel GJ. Comparing the standard EQ-5D three-level system with a five-level version. *Value Health*. 2008;11(2):275-284. https://doi.org/10.1111/j.1524-4733.2007.00230.x

Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer*. 2019;5:5. https://doi.org/10.1038/s41523-018-0097-z

Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998. https://doi.org/10.1200/JCO.20.02514

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481. https://doi.org/10.2307/2281868

DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med*. 1994;13(13-14):1341-1352; discussion 1353-1356. https://doi.org/10.1002/sim.4780131308

Lei JT, Anurag M, Haricharan S, et al. Endocrine therapy resistance: new insights. *Breast*. 2019;48 Suppl 1(suppl_1):S26-S30. https://doi.org/10.1016/S0960-9776(19)31118-X

Levit LA, Peppercorn JM, Tam AL, et al. Ethical Framework for Including Research Biopsies in Oncology Clinical Trials: American Society of Clinical Oncology Research Statement. *J Clin Oncol.* 2019;37:2368-2377. https://doi.org/10.1200/JCO.19.01479

Loibl S, Marmé F, Martin M, et al. Abstract GS1-02: phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancer and with high relapse risk after neoadjuvant chemotherapy (NACT): first results from PENELOPE-B [abstract]. *Cancer Res.* 2021;81(suppl_4). https://doi.org/10.1158/1538-7445.SABCS20-GS1-02

Mariotti V, Khong H, Soliman H, et al. Abstract P5-11-10: abemaciclib following palbociclib in metastatic breast cancer (MBC): characteristics of patients (pts) with durable response [abstract]. *Cancer Res*. 2020;80(suppl_4):P5-11-10. https://doi.org/10.1158/1538-7445.SABCS19-P5-11-10

Martin JM, Handorf EA, Montero AJ, Goldstein LJ. Abstract PS10-15: analysis of systemic therapies following progression on frontline CDK4/6-inhibitor therapy [abstract]. *Cancer Res*. 2021;81(suppl_4). https://doi.org/10.1158/1538-7445.SABCS20-PS10-15

Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2021;22(2):212-222. https://doi.org/10.1016/S1470-2045(20)30642-2

McCartney A, Migliaccio I, Bonechi M, et al. Mechanisms of resistance to CDK4/6 inhibitors: potential implications and biomarkers for clinical practice. *Front Oncol*. 2019;9:666. https://doi.org/10.3389/fonc.2019.00666

[NCI] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Published November 27, 2017. Accessed October 07, 2019. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

[NCCN] National Comprehensive Cancer Network. Clinical practice guidelines in oncology for breast cancer. Version 4.2021. Accessed May 17, 2021. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.

Pickard AS, de Leon MC, Kohlmann T, et al. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. *Med Care.* 2007;45(3):259 263. https://doi.org/10.1097/01.mlr.0000254515.63841.81

Rizzo JD, Somerfield MR, Hagerty KL et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol.* 2008;26(1):132-149. https://doi.org/10.1200/JCO.2007.14.3396

Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncol.* 2021;22(4):489 498. https://doi.org/10.1016/S1470-2045(21)00034-6.

Sammet S. Magnetic resonance safety. *Abdom Radiol (NY)*. 2016;41(3):444-451. https://doi.org/10.1007/s00261-016-0680-4

Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884. https://doi.org/10.1200/JCO.2017.73.7585

Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol*. 2020;6(1):116-124. https://doi.org/10.1001/jamaoncol.2019.4782

Smith TJ, Bohlke K, Lyman GH, et al.; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2015;33(28):3199-3212. https://doi.org/10.1200/JCO.2015.62.3488

Spring LM, Wander SA, Zangardi M, Bardia A. CDK 4/6 inhibitors in breast cancer: current controversies and future directions. *Curr Oncol Rep*. 2019;21(3):25. https://doi.org/10.1007/s11912-019-0769-3

Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. https://doi.org/10.3322/caac.21660

Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomized phase 3 trial. *Lancet Oncol*. 2018;19(7):904-915. https://doi.org/10.1016/S1470-2045(18)30292-4

Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med. 2015*;373(3):209-219. https://doi.org/10.1056/NEJMoa1505270

Verzenio (abemaciclib) [package insert]. Indianapolis, IN. Eli Lilly and Company; 2019.

Verzenios [SmPC]. Utrecht, The Netherlands. Eli Lilly Nederland B.V.; 2018.

von Minckwitz G, Schwedler K, Schmidt M, et al. Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. *Eur J Cancer*. 2011;47(15):2273-2281. https://doi.org/10.1016/j.ejca.2011.06.021

Wander SA, Cohen O, Gong X, et al. The genomic landscape of intrinsic and acquired resistance to cyclin-dependent kinase 4/6 inhibitors in patients with hormone receptor positive metastatic breast cancer. *Cancer Discov*. 2020;10(8):1174-1193. https://doi.org/10.1158/2159-8290.cd-19-1390

Wander SA, Han HS, Zangardi ML, et al. Clinical outcomes with abemaciclib after prior CDK4/6 inhibitor progression in breast cancer: a multicenter experience. *J Natl Compr Canc Netw*. 2021;1-8. https://doi.org/10.6004/jnccn.2020.7662

Weatherman RV, Fletterick RJ, Scanlan TS. Nuclear-receptor ligands and ligand-binding domains. *Annu Rev Biochem*. 1999;68:559-581. https://doi.org/10.1146/annurev.biochem.68.1.559

Wolff AC, Hammond ME, Allison KH, Harvey BE, Mangu PB, Bartlett JM, Bilous M, Ellis IO, Fitzgibbons P, Hanna W, Jenkins RB, Press MF, Spears PA, Vance GH, Viale G, McShane LM, Dowsett M. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2018:142(11):1364-1382

Signature Page for VV-CLIN-050468 v2.0

Approval	PPD 23 08:48:59 GMT+0000

Approval	PPD 00:21 GMT+0000

Signature Page for VV-CLIN-050468 v2.0

Approved on 04 Oct 2023 GMT