Protocol J2J-OX-JZLC Amendment (d)

EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant Plus Abemaciclib in Patients With Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated With Endocrine Therapy

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Approval Date: 31-Jul-2023

CLINICAL PROTOCOL J2J-OX-JZLC

EMBER-3: A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy

Investigational Product:	imlunestrant (LY3484356); abemaciclib (LY2835219)
Protocol Number:	J2J-OX-JZLC
Development Phase:	3
IND #:	145311
EudraCT#:	2021-000079-35
EU trial number:	2023-506786-63-00
Sponsor:	Eli Lilly and Company Indianapolis, IN, USA 46285
Current Version:	Amendment (d)
Document ID:	VV-CLIN-074716

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	*11-Nov-2022*
Amendment b	*17-Aug-2022*
Amendment a	*08-Oct-2021*
Original Protocol	*15-Mar-2021*

Amendment [d]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale of this amendment is to change the initial alpha split for PFS for Arm A versus Arm B in the ITT population and PFS for Arm A versus Arm B in the ESR1-mutation detected population due to external SERD data.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added • Regulatory Agency Identifier Number(s) • Study Population • Ethical Considerations of Benefit/Risk • "Yes" for Data Monitoring Committee	For EU-CTR compliance
1.3. Schedule of Activities	To "Survival Information" row, added "Date of progression on the FIRST post-discontinuation anticancer treatment should be collected"	For clarification
2. Introduction	Added "Introduction/Rationale for Amendment (d): Updating initial alpha allocation for PFS between Arm A and Arm B" paragraph	Addition
6. Study Intervention	Updated the definition of study intervention	For EU-CTR compliance
6.1. Study Intervention(s) Administered	Added • Last row to the table • Packaging and labeling	For EU-CTR compliance
9.2. Sample Size Determination	Updated third, fourth, and fifth paragraphs	Update due to external SERD data
9.4.1. General Considerations	Added the last paragraph regarding handling of missing, unused, and spurious data	For EU-CTR compliance
9.4.3.1. Primary Analyses	Updated second and third paragraphs.	Update due to external SERD data

Section # and Name	Description of Change	Brief Rationale
9.5.2. Efficacy Interim Analyses	Description of the efficacy interim analyses plan was updated in first paragraph, deleted second paragraph, updated third paragraph, and updated the table "Stopping Boundaries for Each Analysis between Arm A and Arm B in the ITT Population Based on the Initial Allocation of Alpha for Illustration"	Update due to external SERD data
10.1.1. Regulatory and Ethical Considerations	Added a bullet point regarding reporting of significant issues related to participant's safety, rights, and data integrity	For EU-CTR compliance
10.1.4. Data Protection	Updated the language	For EU-CTR compliance
10.1.5. Dissemination of Clinical Study Data	Added this section and section numbers of subsequent sections are changed	For EU-CTR compliance
10.6.1. Definition of AE	Replaced the fifth bullet point of "Events Meeting the AE Definition"	For EU-CTR compliance
10.6.6. Regulatory Reporting Requirements	Updated the language in second bullet point	For EU-CTR compliance

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1 Protocol Summary

1.1. Synopsis

Protocol Title: EMBER-3: A Phase 3, Randomized, Open-Label, Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy

Short Title: EMBER-3: A Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with ER+, HER2- Advanced Breast Cancer

Regulatory Agency Identifier Number(s):

IND #:145311

EudraCT#: 2021-000079-35

EU trial number: 2023-506786-63-00

Rationale:

The incorporation of CDK4/6 inhibitors into the first line of ET for locally advanced or metastatic ER+, human epidermal growth factor receptor 2 negative (HER2-) breast cancer has dramatically improved patient outcomes. However, these therapies are not curative, and progression eventually occurs in nearly all patients. Outcomes for subsequent second-line ET are unfortunately poor and remain an area of unmet need (Chia et al. 2008). Orally bioavailable SERDs with improved bioavailability were designed to overcome the PK and pharmacodynamic liabilities of fulvestrant, an intramuscularly administered agent and the only currently approved SERD.

Imlunestrant (LY3484356) is an oral SERD with antitumor activity within multiple preclinical models, including *ESR1*-mutant models, and an acceptable toxicity profile in nonclinical species. Imlunestrant is a potent degrader and selective pure antagonist of both wild type and mutant ERα (encoded for by the gene *ESR1*). Imlunestrant's antitumor activity is enhanced by the combination with abemaciclib, including in *ESR1*-mutant models and palbociclib-resistant cells. Furthermore, imlunestrant has demonstrated tolerability along with preliminary evidence of clinical activity, alone and in combination with abemaciclib.

Study J2J-OX-JZLC (henceforth referred to as EMBER-3) is a Phase 3, randomized, 3-arm study of imlunestrant, Investigator's Choice of Endocrine Therapy of either fulvestrant or exemestane, and imlunestrant plus abemaciclib in patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor. This study will evaluate 2 comparisons: imlunestrant vs Investigator's Choice of Endocrine Therapy; and imlunestrant plus abemaciclib vs imlunestrant.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the PFS of imlunestrant (Arm A) to the standard comparator of Investigator's Choice Endocrine Therapy of either fulvestrant or exemestane (Arm B) in the ITT population • To compare the PFS of Arm A to Arm B in the *ESR1*-mutation detected population • To compare the PFS of imlunestrant plus abemaciclib (Arm C) to imlunestrant (Arm A) in the ITT population	• Investigator-assessed PFS (between Arm A and Arm B) in the ITT population • Investigator-assessed PFS (between Arm A and Arm B) in the *ESR1*-mutation detected population • Investigator-assessed PFS (between Arm C and Arm A) in the ITT population
Secondary	
• To compare OS of Arm A to Arm B in the ITT population • To compare OS of Arm A to Arm B in the *ESR1*-mutation detected population • To compare OS of Arm C to Arm A in the ITT population • To compare other efficacy objectives of Arm A to Arm B, and Arm C to Arm A	• OS between Arm A and Arm B in the ITT population (*key secondary endpoint*) • OS between Arm A and Arm B in the *ESR1*-mutation detected population (*key secondary endpoint*) • OS between Arm C and Arm A in the ITT population *(key secondary endpoint*) • Investigator-assessed ORR, DoR, and CBR • PFS by blinded Independent Review Committee (BIRC)
• To assess the safety and tolerability of each treatment arm	• Including but not limited to AEs, serious AEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0
• To evaluate the effectiveness of Arm A compared to Arm B and Arm C compared to Arm A based on PROs of pain using the Worst Pain NRS	• Time to sustained worsening of the "worst pain" as measured by Worst Pain NRS
• To assess the PK of imlunestrant (Arm A and Arm C) • To assess the PK of abemaciclib and its metabolites (Arm C)	• Plasma concentrations of imlunestrant and abemaciclib

Abbreviations: AE = adverse event; BIRC = blinded Independent Review Committee; CBR = clinical benefit rate; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; ITT = Intention to treat; NCI = National Cancer Institute; NRS = numeric rating scale; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PROs = patient-reported outcomes.

Overall Design

EMBER-3 is a Phase 3 global, randomized, open-label, 3-arm study of imlunestrant as continuous monotherapy (Arm A) Investigator's Choice Endocrine Therapy of either fulvestrant or exemestane (Arm B), and imlunestrant plus abemaciclib (Arm C) in patients with ER+, HER2- locally advanced (not amenable to curative treatment by surgery) or metastatic breast cancer. The study will enroll patients who have been treated with an AI, alone or in combination with a CDK4/6 inhibitor. Prior treatment with a CDK4/6 inhibitor is expected if this treatment is approved and reimbursed, and the Sponsor may elect to limit the enrollment of participants who have NOT received prior treatment with a CDK4/6 inhibitor.

The study will consist of a 28-day *screening phase*; followed by a *treatment phase*; and a *post-treatment phase,* which includes safety, efficacy, and survival follow-up. Investigator's Choice Endocrine Therapy (fulvestrant or exemestane) must be selected prior to randomization.

Patients will be randomized 1:1:1 between the 3 treatment arms of imlunestrant (Arm A), Investigator's Choice Endocrine Therapy (Arm B), or imlunestrant plus abemaciclib (Arm C).

Arm C was added to the study (amendment a) after first patient visit for Arms A and B. Randomization of patients will continue in Arms A and B (1:1) until amendment a is approved and implemented, at which point patients will be randomized 1:1:1 (A:B:C) until the target enrollment for Arm A and Arm B (n=640 in total) is met.

Patients will be randomized using the following stratification factors:

- Previous treatment with any CDK4/6 inhibitor (yes versus no)
- Presence of visceral metastases (yes versus no); visceral includes lung, liver, brain, pleural, and peritoneal involvement
- Region (East Asia versus North America/Western Europe versus Others)

The primary study objectives are to

- compare the PFS of Arm A to Arm B in the ITT population,
- compare the PFS of Arm A to Arm B in the *ESR1*-mutation detected population, and
- compare the PFS of Arm C to Arm A in the ITT population.

To control the overall type I error rate, the PFS hypotheses will be tested hierarchically using a graphical approach. Initially, the overall 1-sided alpha level of 0.025 will be split between PFS for Arm A versus Arm B in the ITT population and PFS for Arm A versus Arm B in the *ESR1*-mutation detected population. PFS for Arm C versus Arm A in the ITT population will be inferentially tested only if the PFS for Arm A versus Arm B in either the ITT population or in the *ESR1*-mutation detected population is statistically significant.

Disclosure Statement: This is a randomized, active treatment study with 3 arms where the patient and investigator will not be blinded.

Study Population:

- Participants must be at least 18 years of age
- Have a diagnosis of ER+, HER2- breast cancer, as defined in the relevant ASCO/CAP Guidelines
- Have locally advanced (not amenable to curative treatment by surgery) or metastatic disease with disease recurrence or progression on an adjuvant AI with or without a CDK-4/6 inhibitor.
- Must be deemed appropriate for treatment with ET.

Number of Participants:

Approximately 860 participants will be enrolled to this study.

Intervention Groups and Duration:

	Arm A Imlunestrant	**Arm B** Investigator's Choice Endocrine Therapy		**Arm C** Imlunestrant + Abemaciclib	
Treatment	Imlunestrant	Fulvestrant	Exemestane	Imlunestrant	Abemaciclib
Dose	400 mg	500 mg	25 mg	400 mg	150 mg
Schedule	QD in 28-day continuous cycles	500 mg on C1D1 and C1D15 and then on Day 1 of a 28-day cycle starting at Cycle 2	QD in 28-day continuous cycles	QD in 28-day continuous cycles	BID in 28-day continuous cycles
Route	Oral	Intramuscular injection of two 250 mg injections	Oral	Oral	Oral

Abbreviations: BID = twice daily; C = cycle; D = day; QD = once daily.

Duration of treatment:

Patients will be treated until disease progression or other discontinuation criteria are met (Section 7.1).

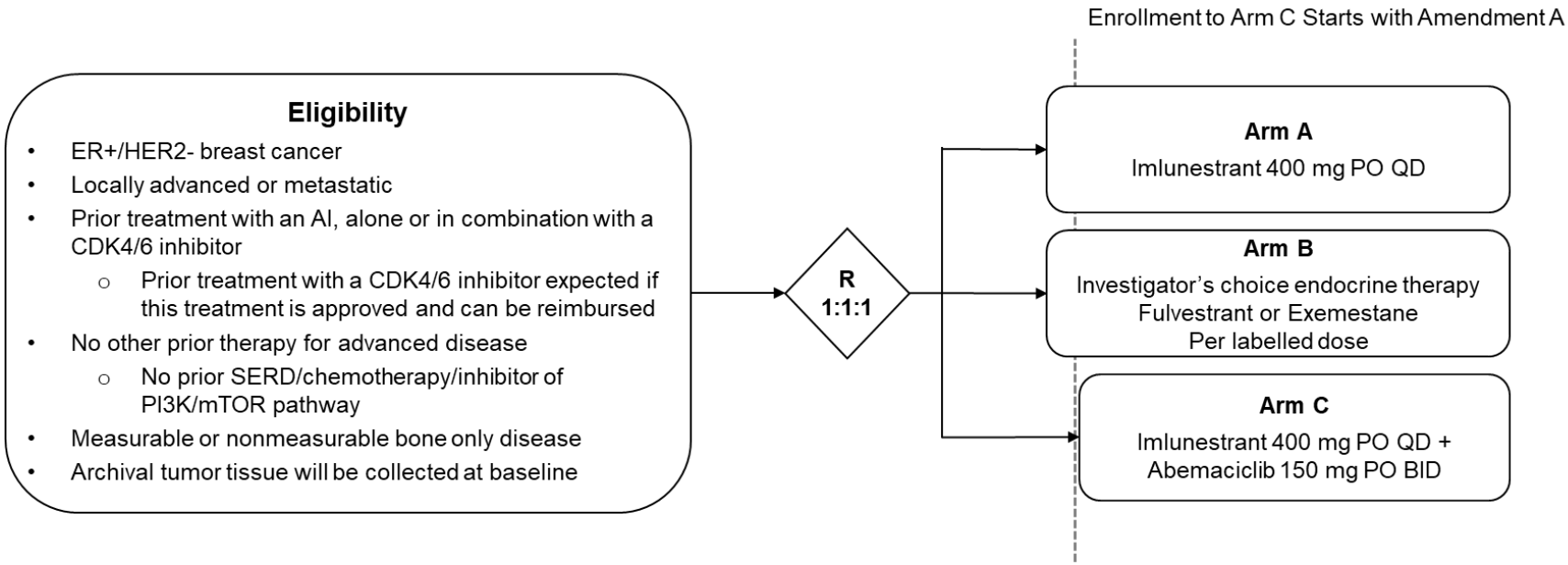
Ethical Considerations of Benefit/Risk:

Given the key anticipated benefits for patients with ER+, HER2- mBC, an incurable disease with a poor prognosis, and limited non-cytotoxic therapeutic options, the potential risks are considered acceptable to evaluate this novel therapy, imlunestrant, as monotherapy or in combination with abemaciclib, in this patient population within this global Phase 3 study.

Data Monitoring Committee: Yes

A DMC will be utilized to assess aggregate efficacy and safety data for this study. Please refer to the DMC charter and Section 6.3 for further information.

1.2. Schema



Note: *ESR1* mutation status will be centrally determined in plasma by Guardant 360 ctDNA assay from a blood draw at baseline.

Treatment administration instructions are detailed in Section 6.1.

Abbreviations: AI = aromatase inhibitor; CDK = cyclin-dependent kinase; ctDNA = Circulating tumor DNA; ER+ = estrogen receptor positive; FPV = first patient visit; HER2- = human epidermal growth factor receptor 2 negative; mTOR = mammalian target of rapamycin; n = number of participants; PI3K = phosphoinositide 3-kinase; PO = orally; QD = once daily; R = randomization; SERD = selective estrogen receptor degrader.

1.3. Schedule of Activities

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Study Entry/ Enrollment	Informed consent form signed	X							Section 10.1.3	Informed consent form must be signed prior to performance of any protocol-specific tests or procedures and prior to randomization
	Inclusion/exclusion evaluation	X							Sections 5.1 and 5.2	
Medical History	Medical history	X							Section 9.4.2.2	• All conditions ongoing and relevant past surgical and medical history should be collected • Malignancy history should be collected regarding disease being assessed for this study, prior cancer treatments, and any history of other malignancy
Physical Examination	Physical exam	X	X		X	X	X		Section 9.4.2.2	• Complete PE including height (at screening only), weight, and review of relevant symptoms at screening • Screening results obtained within 3 days of C1D1 can be used for C1D1 results
	Vital signs	X	X		X	X	X		Section 8.2	• Include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature • Screening results obtained within 3 days of C1D1 can be used for C1D1 results
	ECOG PS	X	X		X	X	X		Section 10.2 Appendix 2	Screening results obtained within 3 days of C1D1 can be used for C1D1 results

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Clinical Tumor Assessment	Tumor measurement (palpable or visible)	X			See Instructions				Section 8.1 and Section 10.3 Appendix 3	• Visible tumor (such as skin lesions) should be documented by photography, and each photographic image of the tumor should include a ruler. If measurable, caliper measurements should be recorded. Images will be collected for central storage for BIRC review • Perform at RECIST response assessment intervals outlined below
Tumor Assessment	Radiologic imaging according to RECIST[b]	X			See Instructions				Section 8.1 and Section 10.3 Appendix 3	• Required for all patients • Perform according to RECIST v1.1 criteria by the same method used at baseline • CT or MRI scan of the chest, abdomen, and pelvis performed with IV contrast when possible[b] • Response assessments should occur at baseline and then at the following intervals relative to Cycle 1 Day 1: every 8 weeks (±4 days) for the first 12 months and then every 12 weeks (±4 days) thereafter, until radiographic disease progression, death, start of a new anticancer therapy or study completion, whichever occurs first. • Perform as scheduled, regardless of any treatment delays or interruptions • Perform within 14 days of clinical progression • A central radiology vendor will be used to collect and store images for BIRC review

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
	X-ray or CT scan with bone windows or MRI	X			See Instructions				Section 8.1 and Section 10.3 Appendix 3	• Required only for patients with RECIST non-measurable bone-only disease, for any lesions identified on bone scintigraphy that are not visible on the chest, abdomen, and pelvis CT or MRI • All such bone lesions are evaluated by directed imaging (X-ray, CT scan with bone windows, or MRI) to enable serial assessment • One or more of these studies (X-ray, CT scan with bone windows, or MRI), identical to the study obtained at baseline, should be performed at the RECIST response assessment intervals outlined above • For patients with new lesions identified by postbaseline bone scintigraphy, targeted assessments by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings • A central radiology vendor will be used to collect and store images for BIRC review

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
	Brain imaging	X			See Instructions				Section 8.1 and Section 10.3 Appendix 3	• Required at baseline for patients without a history of brain metastases: Either a brain CT or brain MRI. Contrast is recommended. • Required at baseline for patients with treated brain metastases: Contrast-enhanced brain MRI is preferred; however, if MRI contrast is contraindicated, then the following are acceptable: MRI (without contrast) or brain CT (recommended with contrast). • Patients with a history of brain metastases must have imaging repeated at the RECIST response assessment intervals outlined above. • A central radiology vendor will be used to collect and store images for BIRC review.

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Tumor Assessment	Bone scintigraphy	X				See Instructions			Section 8.1 and Section 10.3 Appendix 3	• Required for all patients (testing up to 45 days prior to C1D1 may be used for baseline assessment) • Postbaseline bone scintigraphy should occur every 24 weeks (±4 days), with first assessment relative to Cycle 1 Day 1, until radiographic disease progression, death, start of a new anticancer therapy, or study completion, whichever occurs first • Perform as scheduled, regardless of any treatment delays or interruptions • Perform within 14 days of clinical progression • Importantly, RECIST v1.1 emphasizes bone scintigraphy is not adequate to measure bone lesions; however, bone scintigraphy can be used to confirm the presence or disappearance of bone lesions • A central radiology vendor will be used to collect and store images for BIRC review
Patient Diary (Arms A and C)			X		X	X				• Provide patient drug diary on Day 1 of each cycle for patients randomized to Arms A or C. Completed daily by patient • Review at each study visit

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Survival Information							X	X	Section 8.1 and Section 10.3 Appendix 3	• Survival information is collected during both study treatment and at post-discontinuation follow-up • During long-term follow-up, survival information is collected approximately every 12 weeks (±14 days) for the duration of this period. Survival information may be collected in clinic or by contacting the patient or family directly (for example, via telephone). Long-term follow-up data collection may include post-discontinuation anticancer therapies. Date of progression on the FIRST post-discontinuation anticancer treatment should be collected.

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Adverse Event Collection/ CTCAE Grading		X	X		X	X	X	X	Section 8.3	• Collect continuously at every visit and throughout the study • CTCAE Version 5.0 • For long-term follow-up: all SAEs regardless of relationship to study treatment and adverse events possibly related to study treatment will be collected • All adverse events possibly related to study drugs or protocol procedures should be followed until they resolve, are no longer considered to be possibly related, become stable or return to baseline, the patient starts a new therapy, the patient expires, or the patient becomes lost to follow-up. The frequency of evaluation is determined according to the judgment of the investigator
Concomitant Medications		X	X		X	X	X		Section 6.5	• At baseline, record prior and concurrent medications • Record all pre-medications, supportive care, and concomitant medication continuously at every visit and throughout study
Lab/Diagnostic Tests	Coagulation	X							Section 10.4 Appendix 4	• Perform at baseline and as clinically indicated • Local testing

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
	Hematology	X	X	X	X	X	X		Section 10.4 Appendix 4	• Assessments may be performed up to 3 days prior to Day 1 of each cycle • Local testing • Cycles 1 and 2 Day 15 hematology required for Arms A, C only
	Clinical chemistry	X	X	X	X	X	X		Section 10.4 Appendix 4	• Assessments may be performed up to 3 days prior to Day 1 of each cycle Central testing • Cycles 1 and 2 Day 15 clinical chemistry required for Arms A, C only
	FSH and estradiol levels	X				X	X		See Section 5.1 and Section 10.4	• For Screening: local FSH/E2 testing for women <60 years when needed to confirm post-menopausal status • For On study: local estradiol every 3 cycles, starting on Day 1 of Cycle 4 and again at STFU visit, for women whose postmenopausal status is due to GnRH agonist treatment
	Pregnancy test	X					X		Section 10.7 Appendix 7	• Local testing • For Screening: serum pregnancy test required for women of child-bearing potential • For on Study: per local regulations and/or institutional guidelines • For Short-Term Follow-Up: local testing for women of child bearing potential

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
	Fasting lipid testing	X			X	X			Section 10.4 Appendix 4	• Perform at baseline, then every 3 cycles starting on Cycle 3 Day 1 • May be performed ±7 days in relation to Day 1 of relevant cycles • Central testing
Lab/Diagnostic Tests	Local ECG	X	X			X	X		Section 1.3.2	• A local ECG (no replicates required) should be obtained at baseline in all patients • For patients receiving treatment with imlunestrant (Arms A & C): collect single local ECG on Day 1 of Cycles 1, 2, 4 and at the STFU at the time points specified in Section 1.3.2 • Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection
Biomarker, Pharmacokinetic, Pharmacogenetic, Tissue Collection	PK sample		X		X	X			Section 1.3.2	• For patients receiving treatment with imlunestrant (Arms A & C): collect PK samples on Day 1 of Cycles 1, 2, 3 and 4 at the time points specified in Section 1.3.2
	Pharmacogenetic whole blood sample		X						Section 8.7	• Collect once. Sample may be collected anytime if not collected on C1D1 to reduce burden of blood draws on C1D1
	Biomarker plasma sample	X	X		X	X	X		Section 8.8	• Collected during screening; pre-dose on C1D1 and at any time on C2D1; then at any time on Day 1 of each odd cycle beginning with Cycle 3; and lastly at STFU Visit 801

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
	Tumor tissue	X							Section 8.8	• Required for all patients if available • See Section 8.8 for additional instructions
Health Outcomes	PRO		See Instructions				X		Section 1.3.1	• Performed at the time points specified in Section 1.3.1 • See Section 1.3.1 for details of assessment for each instrument
	Hospitalization and ED visits	X	X				X		Section 8.9.9	
	SRE assessment	X	X				X		Sections 8.9.9 & 9.4.7.1	
Study Drug Administration	Imlunestrant		PO QD on Days 1 through 28 of every cycle						Section 6.1	• See Section 6.1 for administration instructions
	Fulvestrant		IM Days 1 and 15 (±3 days) of Cycle 1, then Day 1 (±3 days) of Cycle 2 and beyond						Section 6.1	• Administer per approved label • See Section 6.1 for administration instructions
	Exemestane		PO QD on Days 1 through 28 of every cycle						Section 6.1	• Administered per approved label • See Section 6.1 for administration instructions
	Abemaciclib		PO BID on Days 1 through 28 of every cycle						Section 6.1	• See Section 6.1 for administration instructions

Abbreviations: BID = twice daily; BIRC = blinded independent review committee; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ED = emergency department; FSH = follicular stimulating hormone; IM = intramuscular; MRI = magnetic resonance imaging; PE = physical exam; PK = pharmacokinetics; PO = orally; PRO = patient-

reported outcome; PS = performance status; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; SRE = skeletal-related event: STFU = short-term follow-up.

[a] Short-term follow-up period begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days; the associated study procedures should be performed once at the end of the short-term follow-up period (approximately 30 days after the last dose of study drug). Long-term follow-up period begins the day after the short-term follow-up visit is completed and continues until the patient's death or overall study completion; the associated study procedures are performed approximately every 12 weeks (± 14 days) for the duration of this period beginning 12 weeks after the short-term follow-up visit.

[b] For patients with inoperable locally advanced breast cancer: MRI scan of the breast should occur at baseline and then at the following intervals relative to Cycle 1 Day 1: every 8 weeks (±4 days) for the first 12 months and then every 12 weeks (±4 days) thereafter. For all patients: Tumor assessments, including measurement of visible lesions, CT or MRI scan of the chest, abdomen, and pelvis, should occur at baseline and then at the following intervals with first assessment relative to Cycle 1 Day 1: every 8 weeks (±4 days) for the first 12 months and then every 12 weeks (±4 days) thereafter. It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast whenever possible. If this is not feasible due to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and gadolinium-enhanced MRI of the abdomen/pelvis are encouraged. For patients who discontinue study treatment without objectively measured progressive disease, continue to evaluate tumor response at the following intervals relative to Cycle 1 Day 1: approximately every 8 weeks for the first 56 weeks and thereafter approximately every 12 weeks until radiographic disease progression, death, start of a new anticancer therapy or study completion, whichever occurs first.

[c] Cycle 1 Day 15: For patients assigned to Arms A or C, this visit is only for obtaining protocol-specified laboratory studies. For patients assigned to Arm B who are receiving fulvestrant, this visit is only for administration of the fulvestrant. Cycle 2 Day 15: For patients assigned to Arms A or C, this visit is only for obtaining protocol-specified laboratory studies.

Continued Access SoA for All Patients (see also Section 6.7.1)

	Study Treatment	Extension Period 30-Day Follow-Up[a]		
Visit	**501-5XX**	**901**		
Duration (days)	**28**	**30 ±5**		
Procedure			**Protocol Reference**	**Instructions**
AE Collection	X	X	Section 8.3	Per CTCAE v5.0, for post follow-up, the investigator should only be made aware of collected SAEs related to study regimen or protocol procedures. Collect throughout the study.
Administer study intervention	X		Section 6.1	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 extension period begins after study completion and ends at the end of trial.

1.3.1. Schedule of Assessments for Patient-Reported Outcomes

Instrument	Screening	Cycle 1	Completed at Home during All Cycles until Last Visit (SFU)				Short-Term Follow-Up	Instructions
Visit Window		Day 1	Every Day	Every Week	Every 4 Weeks	Every 8 Weeks		
Worst Pain NRS		X	X				X	Completed at home **daily** by patient on ePRO patient hand-held device, except on C1D1 and STFU visits when it will be administered in the clinic
mBPIsf		X			X		X	Completed at home **every 4 weeks** on ePRO patient hand-held device, except on C1D1 and STFU when it will be administered in the clinic.
PRO-CTCAE: Diarrhea		X		X			X	Completed at home **weekly** on ePRO patient hand-held device, except on C1D1 and STFU when it will be administered in the clinic.
PRO-CTCAE: Injection site pain and swelling				X			X	Screening /Logic question completed electronically **weekly** by the patients receiving fulvestrant only. PRO CTCAE Injection site pain and swelling item will be administered only if the patient has responded "yes" to receiving fulvestrant injection during the 2 weeks prior. Administered at home on ePRO patient hand-held device, except on STFU when it will be administered in the clinic.
EORTC QLQ-C30[a]		X				X	X	Completed at home **every 8 weeks** on ePRO patient hand-held device, except on C1D1 and STFU when it will be administered in the clinic. EORTC QLQ-C30 and EORTC IL 19 instruments will be administered on an alternating schedule such that these are scheduled about 4 weeks apart from each other due to the overlapping items for physical function. The second administration of EORTC QLQ C-30 will occur on C3D1 and then continue every 8 weeks thereafter. During the SFU visit, EORTC QLQ-C30 will be administered.

Instrument	Screening	Cycle 1	Completed at Home during All Cycles until Last Visit (SFU)				Short-Term Follow-Up	Instructions
Visit Window		Day 1	Every Day	Every Week	Every 4 Weeks	Every 8 Weeks		
EORTC IL 19 [a]						X		The first administration of EORTC IL-19 will occur on C2D1, completed electronically by the patient at home, not site-administered, and then **every 8 weeks** thereafter. EORTC IL 19 will not be administered during the STFU visit. EORTC QLQ-C30 and EORTC IL 19 instruments will be administered on an alternating schedule such that these are scheduled about 4 weeks apart from each other due to the overlapping items for physical function.
PGIS		X			X		X	Completed at home **every 4 weeks** on ePRO patient hand-held device, except on C1D1 and SFU when it will be administered in the clinic.
EQ-5D-5L		X				X	X	Completed electronically every **8 weeks** by the patient. Administered at home on ePRO patient hand-held device, except on C1D1 and SFU when it will be administered in the clinic.

Abbreviations: C = cycle; 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; EQ-5D-5L = 5-level-EuroQol; mBPIsf = modified Brief Pain Inventory-short form; NRS = numeric rating scale; PGIS= Patient's Global Impression of Symptoms; PROs = patient-reported outcomes; PRO-CTCAE = Patient Reported Outcomes - Common Terminology Criteria for Adverse Events; STFU = short-term follow-up.

[a] EORTC IL 19 will not be administered during the weeks that EORTC QLQ-C30 is administered due to overlapping items.

1.3.2. Sampling Schedules for Pharmacokinetics

The schedule for PK sampling for patients receiving treatment with imlunestrant (Arm A) or imlunestrant plus abemaciclib (Arm C) on study is summarized in the table below. PK samples collected in Arm A will be analyzed for imlunestrant concentrations. PK samples collected in Arm C will be analyzed for concentrations of both imlunestrant and abemaciclib (and its metabolites). See also fasting requirements for imlunestrant dosing in Section 6.1.

On all PK sampling days (with the exception of Cycle 3 Day 1), patients should take the study drug at the clinic. The date and exact time of collection for each venous blood sample should be documented on the laboratory requisition. Differences from the time specified in the protocol are not considered protocol deviations if samples are collected and accurate dates and times are recorded in a timely manner on the appropriate forms.

Pharmacokinetic Sampling Schedule for Arm A and Arm C

Cycle	Day	PK Sample Number	ECG Sample Number[a]	PK Sampling Time Relative to Imlunestrant Dosing
Screening	Day -28 to Day -1		1	
Cycle 1	Day 1	1	2	2 to 4 hours postdose
Cycle 2	Day 1	2	3	Predose[b]
Cycle 3	Day 1[c]	3		PK draw should occur approximately 3 hours after study drug dose. For flexibility, the patient may take C3D1 dose at home prior to arrival at site.
	Day 1[c]	4		2 ± 0.5 hours after PK Sample Number 3 (at least 5 ± 0.5 hours after taking study drug dose at home)
Cycle 4	Day 1	5	4	Predose[b]
Short-term follow-up	30-Day follow-up		5	

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic.

[a] A local ECG (no replicates required) should be obtained at baseline in all patients, 2 to 4 hours after the imlunestrant dose on Cycle 1 Day 1, pre-imlunestrant dose on Cycle 2 Day 1, and Cycle 4 Day 1, and at the short-term follow-up visit. Predose ECGs should be taken at either 90 (-90) minutes, 60 (-60) minutes, or 30 (-30) minutes. Predose time points are flexible for site convenience.

[b] Predose PK samples should be taken within 90 minutes prior to next dose.

[c] On Cycle 3 Day 1 only, patient may take study drug dose at home before arrival at site. The time of study drug dose intake must be recorded by the patient that day.

2. Introduction

Breast cancer is the most frequent cancer among women and is a major cause of cancer-related deaths worldwide. It is estimated that more than 2 million new cases of breast cancer occurred worldwide in women in 2018 (Bray et al. 2018). Treatment options for women with breast cancer are largely determined by tumor hormone receptor (HR) and HER2 status (Gradishar et al. 2020; Waks and Winer 2019).

Over two-thirds of breast cancers express the ER, which is a key driver of breast cancer initiation and progression. ER+ mBC is incurable and therefore considered a serious and life-threatening disease, with a median OS of only 2 to 3 years (Cardoso et al. 2012; Sledge 2020). For patients with HR+, HER2- status, treatment options include ET given alone or in combination with a CDK4/6 inhibitor (abemaciclib, palbociclib, ribociclib); an mTOR inhibitor (everolimus), or a PI3K inhibitor (alpelisib, for the subset of tumors also harboring select PIK3CA mutations). Alternatively, some patients may receive chemotherapy (for example, capecitabine, docetaxel, paclitaxel, nab-paclitaxel (Waks and Winer 2019; Gradishar et al. 2020) as initial therapy based on aggressiveness at initial presentation, or as salvage therapy following failure of ET-based interventions. However, in most ER+ breast cancers, ER remains an important therapeutic target even after the development of resistance to initial ET and changing the ET backbone has led to improved outcomes, either alone or with other anticancer therapies (Weatherman et al. 1999; Baselga et al. 2012; Turner et al. 2015; Finn et al. 2016; André et al. 2019).

Multiple means of inhibition of ER signaling are already available. These include strategies such as direct ER modulation (tamoxifen), systemic prevention of the conversion of androgens to estrogens using AIs, and SERDs (fulvestrant) that block and degrade the ER. While ET is typically highly effective initially, especially with the incorporation of CDK4/6 inhibitors (Finn et al. 2016; Hortobagyi et al. 2016; Goetz et al. 2017), most patients ultimately relapse and develop acquired ET resistance (Lei et al. 2019). Outcomes for subsequent second-line ET, often with fulvestrant or exemestane, are unfortunately poor and remain an area of unmet need (Chia et al. 2008).

It is now understood that an important mechanism to the development of ET resistance is the acquisition of somatic mutations in the ER gene (*ESR1*) (Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014). These mutations result in a ligand-independent constitutively activated ER, leading to proliferation and decreased sensitivity to ET. These mutations in *ESR1* have been observed in anywhere up to 50% of mBC patients with the rate highest in patients treated with multiple lines of ET (Zundelevich et al. 2020). Importantly, both preclinical and clinical data demonstrate that SERDs can continue to exert antagonistic effects even in the presence of select *ESR1* mutations (Toy et al. 2017, Turner et al. 2020), ultimately leading to downregulation of the constitutively active receptor.

Fulvestrant is currently the only regulatory agency-approved SERD for the treatment of ER+ mBC (Nardone et al. 2019). However, it has limitations. Due to its insoluble nature with poor oral bioavailability and a short intravenous (IV) half-life, fulvestrant needs to be given IM and is

highly dose dependent (Robertson and Harrison 2004; Robertson et al. 2004). Certainly, improved outcomes were observed in patients receiving a dose of 500 mg IM compared to 250 mg IM (Di Leo et al. 2014). Even though doses higher than 500 mg per month may lead to better ER degradation, the IM administration route of fulvestrant limits the amount of fulvestrant that can be given to patients. Moreover, studies have shown that the maximum administrable dose of 500 mg remains insufficient for maximal ER downregulation in patients. Certainly, patients with inadequate ER downregulation to fulvestrant do appear to do significantly worse than those with a greater decrease in ER, as measured by reduction in ER availability on FES-PET (van Kruchten et al. 2015).

Therefore, there is unmet medical need to develop novel ETs, such as oral SERDs to overcome both the resistance and the PK limitations of fulvestrant, to offer improved bioavailability, greater ER-targeting and -degradation capabilities (Nardone et al. 2019).

Introduction/Rationale for Amendment (a): Addition of Study Arm C (Imlunestrant plus Abemaciclib)

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). Additionally, the monarchE trial demonstrated significant and clinically meaningful improvement in IDFS and DRFS with the addition of abemaciclib to adjuvant endocrine therapy (ET) (Johnston et al. 2020).

However, resistance mechanisms to CDK4/6 inhibitor regimens are not well understood and may be multifactorial, including resistance to the ET backbone and/or the CDK4/6 inhibitor. Specifically, tumors that have developed endocrine resistance (e.g., through an *ESR1* mutation, a common mechanism of acquired ET resistance), may still have continued dependence on inhibition of the CDK4 and 6 pathway. Given the safety and tolerability of CDK4/6 inhibitors in combination with ET, there is growing interest in testing the continuation of a CDK4/6 inhibitor beyond progression while switching the ET backbone. In fact, some randomized Phase 2 studies of continued CDK4/6 inhibition are ongoing to address this question (NCT02632045, NCT03147287, NCT03809988). Supporting this hypothesis, there is preclinical data demonstrating synergy of abemaciclib plus fulvestrant in cell lines resistant to CDK4/6 inhibitors (data on file) along with real-world retrospective clinical studies suggesting the benefit of abemaciclib following disease progression on a CDK4/6 inhibitor (Wander et al. 2020, Mariotti et al. 2020, Martin et al. 2020).

Study J2J-OX-JZLC (henceforth referred to as EMBER-3) is a Phase 3, randomized, 3-arm study of imlunestrant, Investigator's Choice of Endocrine Therapy of either fulvestrant or exemestane, and Imlunestrant plus Abemaciclib for patients with ER+, HER2- locally advanced or metastatic breast cancer previously treated with an AI, with or without a CDK4/6 inhibitor. This study will evaluate 2 comparisons: Imlunestrant vs Investigator's Choice of Endocrine Therapy; and Imlunestrant plus Abemaciclib vs Imlunestrant.

Introduction/Rationale for Amendment (b): Addition of the PFS of Arm A to Arm B in the *ESR1*-mutation detected population as a primary endpoint

The primary goals of this trial are to determine whether: imlunestrant prolongs PFS compared to Investigator's Choice of Endocrine Therapy in patients with ER+, HER2- locally advanced or mBC previously treated with an AI with or without a CDK4/6 inhibitor; AND if imlunestrant plus abemaciclib prolongs PFS compared to imlunestrant monotherapy (inferentially tested ONLY if the PFS between Arm A and Arm B is statistically significant).

It is well understood that a proportion (up to approximately 50%) of the unselected enrolled population (ITT population) will have an *ESR1*-mutation detected at baseline (*ESR1*-mutation detected population) (Zundelevich et al. 2020). Analyses in this subpopulation were already prespecified in the initial study protocol. However, with this amendment (amendment b), the analysis of PFS in the *ESR1*-mutation detected population now will be elevated to a primary endpoint, based on evolving data among the novel SERD class showing increased clinical benefit with *ESR1*-mutation enrichment (Bidard et al. 2022). With the proposed statistical methodology to adjust for multiplicity, the trial will be considered to have met its primary objective (for the Arm A to Arm B comparison) if imlunestrant is superior to Investigator's Choice of Endocrine Therapy in PFS in either all patients (ITT) OR in patients with an *ESR1*-mutation detected (*ESR1*-mutation detected population).

Introduction/Rationale for Amendment (c): Increasing the sample size for PFS between Arm A and Arm B

In this amendment, the total sample size for Arm A and Arm B has been increased to approximately 640 participants (320 in each arm). The primary analysis of PFS between Arm A and Arm B in the ITT population will be conducted when approximately 480 events have been observed (maintaining the same censoring rate of 25% as before). With a total of 480 events, the statistical power has been increased from 80% to 89% assuming a target hazard ratio of 0.74. Correspondingly, the required number of events for PFS between Arm A and Arm B in the *ESR1*-mutation detected population has also been increased from approximately 150 to 192, resulting in increased statistical power (from 80% to 90%) for this endpoint as well.

Additionally, all three arms will be closed at the same time (once the target enrollment for Arm A and Arm B is met). The estimated total sample size across all three arms has increased from approximately 800 to 860 under the updated enrollment assumptions.

Introduction/Rationale for Amendment (d): Updating initial alpha allocation for PFS between Arm A and Arm B

In this amendment, the initial alpha allocation for PFS between Arm A and Arm B in the ITT population (H_1) and PFS between Arm A and Arm B in the *ESR1*-mutation detected population (H_2) is updated from 0.02 and 0.005 to 0.005 and 0.02, respectively. This update is based on the external data of oral SERDs in patients with recurrent ER+ HER2 negative breast cancer where clinically and statistically meaningful improvement in PFS has been primarily driven by the

ESR1-mutation detected population (Bidard et al. 2022). In addition, the second interim analysis for efficacy for H_1 (interim 2) has been removed since the timing of interim 2 is projected to be closer to the timing of the final analysis based on the updated enrollment projection.

2.1. Study Rationale

Imlunestrant (Arm A)

Imlunestrant is an orally bioavailable, pure ER antagonist, and potent ER degrader, developed to address the limitations of existing SERD therapy. Specifically, imlunestrant has favorable pharmacologic and PK properties designed to support continuous ER inhibition throughout the dosing period, with a large volume of distribution and high intratumoral accumulation compared to plasma (exposures 12- to 56-fold higher in tumor than plasma in preclinical models). Imlunestrant has shown antitumor activity within multiple preclinical models, including *ESR1*-mutant models, along with an acceptable toxicity profile in nonclinical species (see the IB for further details on the preclinical package).

In the Phase 1a/1b study (J2J-MC-JZLA, NCT04188548, EMBER), imlunestrant has shown acceptable safety with the most common TEAEs possibly related to study drug including nausea, fatigue, and diarrhea. Importantly, imlunestrant has demonstrated preliminary evidence of clinical activity with a clinical benefit rate of 48% in patients with ER+ HER2- mBC, including in those previously treated with fulvestrant and CDK4/6 inhibitors (Jhaveri et al. 2021).

Additional information pertaining to nonclinical and clinical safety, efficacy, and PK of imlunestrant may be found in the IB.

Imlunestrant plus Abemaciclib (Arm C)

Abemaciclib is a CDK4/6 inhibitor with proven benefit in PFS and OS in CDK4/6-naïve patients with ER+ HER2- MBC when combined with ET (Spring et al. 2019; Sledge et al. 2020). Along with this, preclinical and limited clinical data also suggest benefit of abemaciclib in a CDK4/6-pre-treated context. (Wander et al. 2020, Mariotti et al. 2020, Martin et al. 2020).

Imlunestrant's antitumor activity is enhanced by the combination with abemaciclib. Importantly, imlunestrant has shown strong synergy or additivity in in vitro combination studies with abemaciclib, along with good tolerability and enhanced efficacy with abemaciclib in MCF7 and T47D *ESR1*-wild type breast cancer xenograft model and in an *ESR1*-mutant Y537S breast cancer PDX model. Additionally, the combination of abemaciclib plus imlunestrant synergistically inhibits growth in palbociclib-resistant cells, accompanied by decreased Ki-67 (a marker of proliferation) and increased senescence and apoptosis (data on file).

In the EMBER (J2J-MC-JZLA) study, 4 cohorts of the phase 1b included imlunestrant plus abemaciclib combination treatment regimens. The combination, at the proposed doses, has shown an acceptable safety profile. The overall safety profile was generally consistent with expectations for an abemaciclib plus ET combination, with the most common TEAEs observed including diarrhea, nausea, vomiting, fatigue, decreased appetite and neutropenia.

Additional information pertaining to the clinical safety, efficacy, and PK of imlunestrant plus abemaciclib may be found in the imlunestrant IB.

2.2. Background

As described in Section 2, there remains an unmet medical need for novel, improved, and tolerable ETs for the management of ER+, HER2- mBC, that can overcome the PK and resistance limitations of ETs currently used in the clinic. To this end, promising clinical data have been observed with the oral SERD, imlunestrant, in heavily pretreated ER+ mBC patients. Along with this, abemaciclib has well established clinical benefit in CDK4/6-naïve patients in the 1st and 2nd line setting and has the potential for benefit in CDK4/6-pre-treated patients (Sections 2 & 2.1). The clinical and the preclinical results outlined in Section 2.1 support further investigation of imlunestrant and imlunestrant plus abemaciclib for patients with ER+, HER2- locally advanced or mBC.

The purpose of this study, in patients with ER+, HER2- locally advanced or mBC previously treated with an AI with or without a CDK4/6 inhibitor, is to determine whether: imlunestrant prolongs PFS compared to Investigator's Choice of Endocrine Therapy; and if imlunestrant plus abemaciclib prolongs PFS compared to imlunestrant monotherapy.

Patient randomization within this study will be stratified by known prognostic factors (see Section 4.1 for further details) to reduce the potential for bias and improve the power of the analyses. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. See Sections 6.2.3 and 9.4.2 for further description.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

The clinical safety experience from the EMBER study is described in Section 2.1 with additional details described in the IB. Imlunestrant monotherapy was well tolerated with the majority of observed AEs being low grade, reversible, monitorable and manageable, and the safety profile is consistent with that expected based on imlunestrant mechanism of action and the patient population being treated. Similarly, available clinical data for imlunestrant plus abemaciclib have shown the combination to have a manageable safety profile with the majority of observed events being low grade and expected based on prior abemaciclib plus ET combination experience.

Imlunestrant toxicology studies demonstrate an acceptable safety profile, with toxicities that are generally monitorable and/or reversible and are clinically manageable in the EMBER-3 patient population. The toxicity of imlunestrant has been evaluated in a comprehensive series of

nonclinical safety studies, including repeat-dose toxicology studies in Sprague-Dawley rats and cynomolgus monkeys, genetic toxicity, and phototoxicity studies.

Potential toxicities identified in nonclinical studies include

- effects on female reproductive organs, including ovarian follicular cysts and atrophy of the epithelium of the uterus, cervix, and vagina
- hematological changes, namely increased white blood cells
- decreased lymphoid cellularity in lymphoid organs
- renal effects, such as tubular degeneration at non-tolerated doses in rats
- hepatic effects, such as increased liver enzymes lacking morphological correlation
- gastrointestinal effects including abnormal feces
- phototoxicity, based on an in vitro study
- chromosomal damage, based on an in vitro study (not observed in the in vivo study).

Non-reproductive in vivo toxicology findings demonstrated partial to full reversibility after a 2-week recovery period (evaluated in rats). Female reproductive tract findings have similarly been observed with other approved agents, known to antagonize or degrade the ER, including tamoxifen and fulvestrant. To mitigate the risk of pharmacologically mediated reproductive and developmental toxicity, women of childbearing potential (WOCBP) that enroll in EMBER-3 will:

- Have a negative pregnancy test prior to starting study
- Agree to use highly effective contraception prophylaxis for up to 6 months after the last dose of imlunestrant (also applies to male participants)
- Agree to use hormone suppression initiated at least 28 days prior to study treatment with a gonadotropin-releasing hormone agonist such as goserelin or leuprolide
- Receive guidance regarding potential reproductive and developmental toxicities in informed consent documents

Assessment of the potential overlapping toxicities of the combination regimen imlunestrant and abemaciclib based on current non-clinical and clinical data are considered to be:

- increased liver enzymes
- gastrointestinal effects
- increased susceptibility to infections
- reproductive and developmental toxicity

The potential overlapping toxicities identified are expected to be reversible on discontinuation of study drug and/or investigational product and, therefore, readily managed in clinical practice.

The risk to subjects in this Phase 3 trial will be minimized by compliance with the eligibility criteria, study procedures, close clinical monitoring (including regular hematological and chemistry testing), recommendations for concomitant medications, guidance for prohibited medications, and dose adjustments. Patients will be monitored using clinical safety laboratory tests as described in Section 8.2. Appropriate AE management, safety assessments, and on-study monitoring are detailed in Sections 6.6, 8.2, and 1.3 (SoA), respectively. Hepatic and renal function are regularly monitored throughout the study by means of measurement of chemistry values. Increased susceptibility to infection will be monitored through regular hematology monitoring.

Patients will also be advised to use sunscreen if out in direct sunlight, to reduce the possibility of phototoxicity.

These activities will enable appropriate investigator oversight, including identification and management of AEs. Should the risk profile change as more information becomes available, additional testing and/or evaluations, and adjustments to the dose of may be implemented. Refer to Section 4.3 for the justification of the selected therapy doses.

More detailed information about the known and expected benefits, risks, reasonably expected adverse events, SAEs, and safety profiles of imlunestrant and abemaciclib can be found in the latest versions of the respective IBs.

Detailed information about the known and expected benefits and risks of the SOC approved agents, fulvestrant and exemestane, may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

2.3.2. Benefit Assessment

In patients with ER+, HER2- locally advanced or mBC previously treated with an AI, with or without a CDK4/6 inhibitor, treatment with imlunestrant may result in an improved clinical benefit compared to Investigator's Choice of Endocrine Therapy (fulvestrant or exemestane); and treatment with imlunestrant plus abemaciclib may result in an improved clinical benefit compared to imlunestrant. All patients enrolled in this trial will receive an active therapy, either the investigational agent, imlunestrant alone or in combination with abemaciclib or an approved ET that is SOC (Section 2, Introduction).

Based on preclinical and preliminary clinical data (see Sections 2.1 and 2.2), treatment with imlunestrant is expected to be well tolerated and to delay disease progression compared to Investigator's Choice of ET; and treatment with imlunestrant plus abemaciclib is expected to further improve upon the benefit seen with imlunestrant as a single agent and to be well tolerated.

Patients receiving imlunestrant may also benefit from increased convenience and less pain associated with monthly IM fulvestrant injections.

2.3.3. Overall Benefit: Risk Conclusion

Given the key anticipated benefits for patients with ER+, HER2- mBC, an incurable disease with a poor prognosis and limited non-cytotoxic therapeutic options, the potential risks are considered acceptable to evaluate this novel therapy, imlunestrant, as monotherapy or in combination with abemaciclib, in this patient population within this global Phase 3 study.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the PFS of imlunestrant (Arm A) to the standard comparator of Investigator's Choice Endocrine Therapy of either fulvestrant or exemestane (Arm B) in the ITT population • To compare the PFS of Arm A to Arm B in the *ESR1*-mutation detected population • To compare the PFS of imlunestrant plus abemaciclib (Arm C) to imlunestrant (Arm A) in the ITT population	• Investigator-assessed PFS (between Arm A and Arm B) in the ITT population • Investigator-assessed PFS (between Arm A and Arm B) in the *ESR1*-mutation detected population • Investigator-assessed PFS (between Arm C and Arm A) in the ITT population
Secondary	
• To compare OS of Arm A to Arm B in the ITT population • To compare OS of Arm A to Arm B in the *ESR1*-mutation detected population • To compare OS of Arm C to Arm A in the ITT population • To compare other efficacy objectives of Arm A to Arm B, and Arm C to Arm A	• OS between Arm A and Arm B in the ITT population (*key secondary endpoint*) • OS between Arm A and Arm B in the *ESR1*-mutation detected population (*key secondary endpoint*) • OS between Arm C and Arm A in the ITT population *(key secondary endpoint*) • Investigator-assessed ORR, DoR, and CBR • PFS by blinded Independent Review Committee (BIRC)
• To assess the safety and tolerability of each treatment arm	• Including but not limited to AEs, serious AEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0
• To evaluate the effectiveness of Arm A compared to Arm B and Arm C compared to Arm A based on PROs of pain using the Worst Pain NRS	• Time to sustained worsening of the "worst pain" as measured by Worst Pain NRS
• To assess the PK of imlunestrant (Arm A and Arm C) • To assess the PK of abemaciclib and its metabolites (Arm C)	• Plasma concentrations of imlunestrant and abemaciclib
Exploratory	
• To assess exploratory clinical parameters of Arm A compared to Arm B, and Arm C compared to Arm A	• Time to progressive bone metastases • Time to first SRE (defined as either pathological fracture, spinal cord compression, radiation to the bone, or surgery to the bone) • TTC • CFS • PFS2 (from randomization to disease progression on the next line of treatment or death) • Time to worsening of ECOG PS of ≥2

Objectives	Endpoints
• To explore other PRO and HRQOL parameters of Arm A compared to Arm B, and Arm C compared to Arm A	• Time to worsening of physical function as measured by the physical function score of EORTC IL 19 • Change from baseline as measured by EORTC QLQ-C30 and EQ-5D-5L • Incidence of AE using the PRO-CTCAE item for diarrhea • Change from baseline as measured by the PGIS-Cancer Symptoms
• To compare clinical efficacy parameters of Arm C to Arm B	• PFS • OS
• To explore potential biomarkers related to the ER pathway and/or the pathogenesis of breast cancer	• Biomarker results and efficacy outcomes

Abbreviations: AE = adverse event; BIRC = blinded Independent Review Committee; CBR = clinical benefit rate; CFS = chemotherapy-free survival; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = Circulating tumor DNA; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; 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; EQ-5D-5L = 5-level-EuroQol; ER = estrogen receptor; HRQOL = Health Related Quality of Life; ITT = Intention to treat; NCI = National Cancer Institute; NRS = numeric rating scale; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGIS = Patient's Global Impression of Symptoms; PK = pharmacokinetics; PROs = patient-reported outcomes; PS = performance status; SRE = skeletal-related event; TTC = time to chemotherapy.

4. Study Design

4.1. Overall Design

EMBER-3 is a Phase 3 global, randomized, open-label confirmatory study for patients with ER+, HER2- locally advanced (not amenable to curative treatment by surgery) or mBC, who have been treated with an AI, alone or in combination with a CDK4/6 inhibitor. Prior treatment with a CDK4/6 inhibitor is expected if this treatment is approved and reimbursed and the Sponsor may elect to limit the enrollment of participants who have NOT received prior treatment with a CDK4/6 inhibitor.

Participants will be randomized 1:1:1 between 3 treatment arms (Arm A: Arm B: Arm C) and will be treated until disease progression or other discontinuation criteria are met (Section 7.1).See also schema (Section 1.2)

- Arm A: Imlunestrant 400 mg orally QD on Days 1 to 28 of a 28-day cycle
- Arm B: Investigator's Choice Endocrine Therapy
  - Exemestane 25 mg orally QD on Days 1 to 28 of a 28-day cycle **OR**
  - Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond
- Arm C: Imlunestrant + Abemaciclib
  - Imlunestrant 400 mg orally QD on Days 1 to 28 of a 28-day cycle
  - Abemaciclib 150 mg orally BID on Days 1 to 28 of a 28-day cycle

Arm C was added to the study (amendment a) after first patient visit for Arms A and B. Randomization of participants will continue in Arms A and B (1:1) until amendment a is approved and implemented, at which point participants will be randomized 1:1:1 (A:B:C) until the target enrollment for Arms A and B (a total number of approximately 640 participants) is met.

The study will consist of a 28-day *screening phase*; followed by a *treatment phase*; and a *post-treatment phase,* which includes safety, efficacy, and survival follow-up. Investigator's Choice Endocrine Therapy (fulvestrant or exemestane) must be selected prior to randomization.

Participants will be randomized using the following stratification factors:

- previous treatment with any CDK4/6 inhibitor (yes versus no)
- presence of visceral metastases (yes versus no); visceral includes lung, liver, brain, pleural, and peritoneal involvement, and
- region (East Asia versus North America/Western Europe versus Others).

The primary study objectives are to

- compare the PFS of Arm A to Arm B in the ITT population
- compare the PFS of Arm A to Arm B in the *ESR1*-mutation detected population, and
- compare the PFS of Arm C to Arm A in the ITT population.

To control the overall type I error rate, a graphical approach will be applied to test these PFS hypotheses hierarchically. Initially, the overall 1-sided alpha level of 0.025 will be split between PFS for Arm A versus Arm B in the ITT population and PFS for Arm A versus Arm B in the

ESR1-mutation detected population. PFS for Arm C versus Arm A in the ITT population will be inferentially tested only if the PFS for Arm A versus Arm B in either the ITT population or the *ESR1*-mutation detected population is statistically significant. Further details are provided in Section 9 .

- The primary analysis of PFS between Arm A and Arm B in the ITT population will be performed after approximately 480 investigator-assessed PFS events have been observed in Arm A and Arm B.
- The primary analysis of PFS between Arm A and Arm B in the *ESR1*-mutation detected population will be performed after approximately 192 investigator-assessed PFS events have been observed in the *ESR1*-mutation detected subset (or 80% of the participants in this subset have experienced an event, whichever is earlier) in Arm A and Arm B.
- The primary analysis of PFS between Arm C and Arm A will be performed after approximately 248 investigator-assessed PFS events have been observed among the participants concurrently randomized to Arm A and Arm C.

Under the enrollment assumptions, it is estimated that a total of approximately 860 participants (320 in Arm A, 320 in Arm B, and 220 in Arm C) will be enrolled to this study. Details on sample size determination (including the enrollment assumptions) and statistical considerations are described in Section 9.

Please refer to Section 1.2 for a study schema.

4.2. Scientific Rationale for Study Design

The overall rationale for the study design is described in Section 2.2, and statistical considerations are described in Section 9. Dose selection and justification details can be found in Section 4.3 (Justification for Dose).

4.3. Justification for Dose

Imlunestrant

The dose of imlunestrant monotherapy and in combination with abemaciclib used in this study will be 400 mg given orally once daily (see table in Section 6.1).

Preclinical data supporting the selection of the starting dose of imlunestrant for the EMBER study is detailed in the imlunestrant IB. In short, in in vivo target inhibition studies, imlunestrant, dosed at 10 mg/kg in mice, showed sustained and prolonged inhibition of PGR α expression, a transcriptional target and pharmacodynamic biomarker of Erα, of more than 75% inhibition of PGR for up to 96 hours. Based upon the preclinical PK and pharmacodynamic modeling performed in both wildtype and *ESR1* mutant xenograft models, the in vivo plasma EC80 range for PGR inhibition was predicted to be 17-28 ng/mL. Clinical doses for the Phase 1a dose escalation study (EMBER) were based on predicted human PK, assuming similar PK and pharmacodynamic relationships between species. Average clinical doses of 200 mg QD (80% prediction interval of 100–750 mg QD) were thus predicted to achieve 80% PGR inhibition, the level of inhibition associated with efficacious doses in mouse xenograft studies.

During Phase 1 dose escalation, imlunestrant was administered at doses ranging from 200 mg QD to 1200 mg QD. PK data obtained during dose escalation demonstrated that at doses of 200 mg QD or higher, steady-state plasma concentrations of imlunestrant exceeded the EC80

range calculated from xenograft efficacy models, suggesting that predicted efficacious concentrations would be reached at these doses. Based on the totality of efficacy, clinical PK, and safety data of all enrolled patients (detailed in the IB), the Sponsor determined that the recommended Phase 2 dose of imlunestrant is 400 mg QD.

As previously described in Section 2.1, the proposed doses of imlunestrant 400 mg QD and abemaciclib 150 mg BID demonstrated an acceptable safety profile. In addition, despite the potential for a drug-drug interaction between abemaciclib and imlunestrant based on in vitro data (see Section 6.5), preliminary PK data from EMBER indicate that abemaciclib concentrations are within the normal range of those in monotherapy studies (Patnaik et al 2016).

Therefore, the imlunestrant dose of 400 mg QD in combination with abemaciclib 150 mg BID has been selected as the dose in this study.

Fulvestrant

The dose of fulvestrant (500 mg intramuscularly on Days 1 and 15 of Cycle 1 of a 28-day cycle, then on Day 1 of Cycle 2 and beyond) was selected for this study, as this is the recommended doses in patients with mBC based on tolerability, efficacy, and PK (fulvestrant package insert). Further justification for dose may be found in the corresponding Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

Exemestane

The QD dose of 25 mg of exemestane was selected for this study, as this is the recommended doses in patients with mBC based on tolerability, efficacy, and PK (exemestane US package insert). Further justification for dose may be found in the corresponding Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

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 pivotal 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). Further support of the abemaciclib dose in combination with imlunestrant can be found in Section 2.1 and the imlunestrant IB.

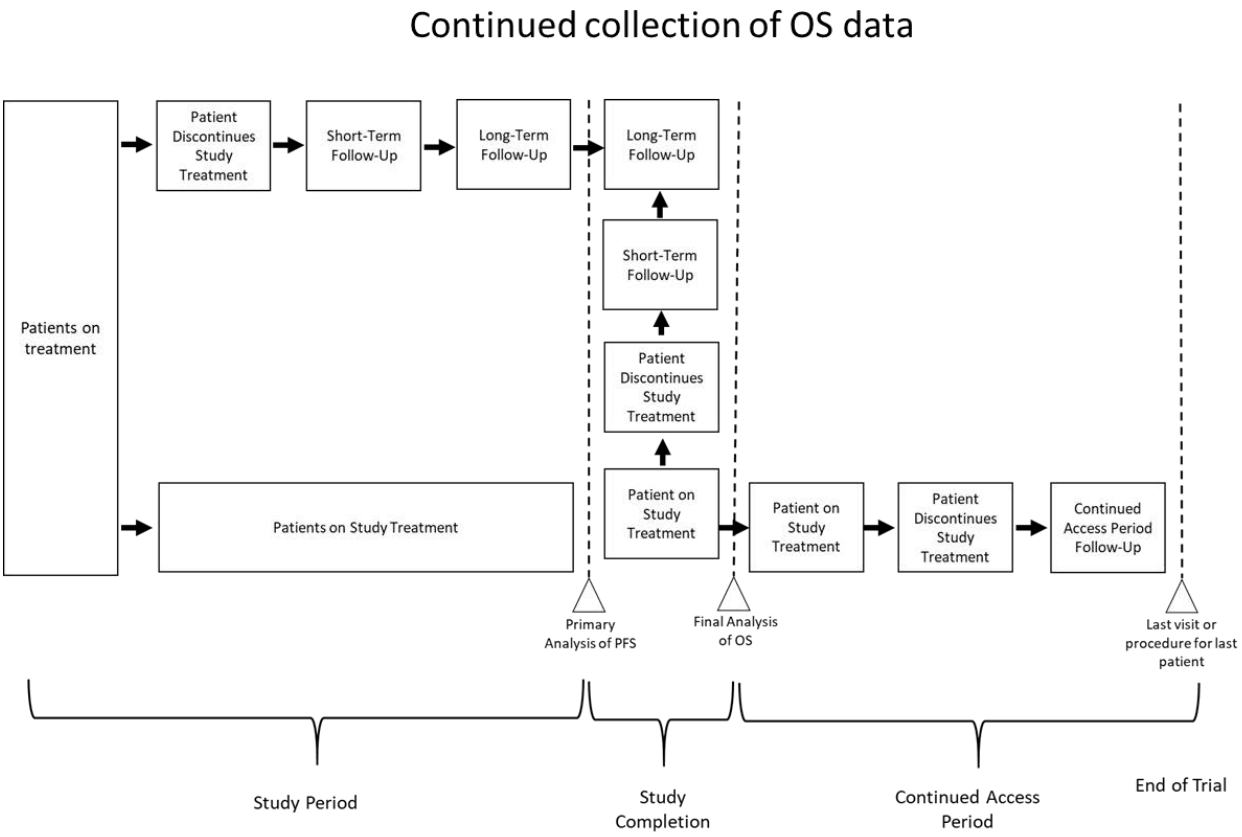
Refer to the abemaciclib IB for additional details.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial globally. 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 Extension Period Diagram below) as determined by the Sponsor. Investigators will continue to follow the study schedule for all patients until notified by the Sponsor that study completion has occurred.

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

Study Period and Extension Period Diagram



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

5. Study Population

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

5.1. Inclusion Criteria

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

1. Participant must be at least 18 years of age
2. Have a diagnosis of ER+, HER2- breast cancer
    a. to fulfill the requirement for ER+ disease, a breast cancer must express the ER by immunohistochemistry, as defined in the relevant ASCO/CAP Guidelines (Allison et al. 2020)
    b. to fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either immunohistochemistry (IHC) or in-situ hybridization as defined in the relevant ASCO/CAP Guidelines (Wolff et al. 2018). Although not required as a protocol procedure, a patient with a new metastatic lesion should be considered for biopsy whenever possible to reassess HER2 status prior to study entry if clinically indicated
3. Have locally advanced (not amenable to curative treatment by surgery) or metastatic disease and **fulfill 1 of the following criteria (3a-c) below**.
    Note 1: Patients are expected to have received prior treatment with a CDK4/6 inhibitor if this treatment is approved and can be reimbursed.
    Note 2: During the course of the trial, the Sponsor may elect to limit the enrollment of participants who have NOT received prior treatment with a CDK4/6 inhibitor.
    a. relapsed with evidence of progression while on or within 12 months of completion of (neo)adjuvant aromatase inhibitor (AI), alone or in combination with a CDK4/6 inhibitor, with no treatment for advanced disease.
        Note: Patients relapsing on or within 12 months of completion of (neo)adjuvant tamoxifen, alone or in combination with a CDK4/6 inhibitor are not eligible.
    b. relapsed with evidence of progression >12 months from completion of (neo)adjuvant ET (ET, tamoxifen, or AI), with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor.
        Note 1: Patients should not have relapsed on or within 12 months of completion of (neo)adjuvant ET (with tamoxifen or an AI).
        Note 2: Patients may not have received any other prior therapy (other than the aforementioned: AI, alone or in combination with a CDK4/6 inhibitor) in the advanced/metastatic setting.
    c. presented de novo with metastatic disease, with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor.
        Note: Patients may not have received any other prior therapy (other than the aforementioned: AI, alone or in combination with a CDK4/6 inhibitor) in the advanced/metastatic setting.
4. Must be deemed appropriate for treatment with ET.

5. If female, have a postmenopausal status due either surgical/natural menopause or ovarian function suppression (OFS) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin or leuprolide (received monthly and initiated at least 28 days prior to Cycle 1 Day 1).

   Note: Participants established on a less frequent (i.e. 3-month) GnRH agonist administration schedule will be permitted, if considered by the investigator to have adequate OFS based on serial estradiol assessments.

   Postmenopausal due to surgical/natural menopause requires at least 1 of the following:
   a. prior bilateral oophorectomy
   b. age ≥60 years
   c. age <60 years, amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression), and FSH and estradiol levels in the postmenopausal range using local laboratory thresholds.
6. If female and postmenopausal status is due to ovarian suppression, participants must have a negative serum pregnancy test at baseline (within 14 days prior to enrollment) and agree to use highly effective, medically approved precautions to prevent pregnancy (see Section 10.7 Appendix 7) during the study and for 6 months (2 years for patients receiving fulvestrant) following the last dose of study treatment
7. If male, must agree to use the following:
   a. hormone suppression (initiated at least 28 days prior to Cycle 1 Day 1) with a gonadotropin-releasing hormone agonist such as goserelin or leuprolide

      Note: Participants established on a less frequent (i.e. 3-month) GnRH agonist administration schedule will be permitted, if considered by the investigator to have adequate hormone suppression.
   b. highly effective methods of birth control and to not donate sperm during the study and for at least 6 months (2 years for patients receiving fulvestrant) following the last dose of study drug(s), or for the duration specified in country requirements, whichever is longer
8. Have one of the following as defined by RECIST v1.1 (Eisenhauer et al. 2009; Section 10.3 Appendix 3):
   - Measurable disease
   - Non-measurable bone-only disease. Non-measurable bone-only disease may include any of the following:
     i. Blastic bone lesions (also known as sclerotic bone lesions)
     ii. Lytic bone lesions without a measurable soft tissue component
     iii. Mixed lytic-blastic bone lesions without a measurable soft tissue component
9. Have a Performance Status of 0 or 1 on the Eastern Cooperative Oncology Group scale (Oken et al. 1982)

10. Have adequate organ function as defined in table below

System	Laboratory Value
Renal	
Serum creatinine or,	<1.5× ULN **OR**
Measured creatinine clearance or,	≥50 mL/min
Calculated creatinine clearance	(See Section 10.5 Appendix 5)
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥9 g/dL
Note: transfusions to increase a patient's hemoglobin level 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	≤1.5× ULN (Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times 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.

11. Have discontinued previous therapies for cancer prior to receiving study drug, 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:
    a. for myelosuppressive agents (for example, CDK4/6 inhibitors): at least 21 days
    b. for nonmyelosuppressive agents (for example, Endocrine Therapy): 7 days or 5 half-lives, whichever is shorter
    c. for investigational agents: 28 days or 5 half-lives, whichever is shorter
12. Patients must be able to swallow capsules/tablets
13. Are willing to participate for the duration of the study and to follow study procedures
14. Capable of giving signed informed consent as described in Section 10.1 Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria applies:

15. Have received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, any investigational-ER-directed therapy (including SERDs

and non-SERDs), any PI3K-, mTOR-, or AKT-inhibitor. Patients who have progressed on prior exemestane treatment must not receive exemestane if randomized to the control arm.

16. Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study
17. Have inflammatory breast cancer
18. Patients with known pathogenic germline mutations who are appropriate for treatment with a PARP inhibitor, in regions where these therapies are approved and available, are not eligible for this study.
19. Have visceral crisis, lymphangitic spread within the lung, or any evidence of leptomeningeal disease. 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
20. Have symptomatic or untreated brain metastasis. Patients with treated brain metastases are eligible for this study if they completed prior therapy (including radiation and/or surgery) ≥28 days prior to first dose of study treatment and are not receiving corticosteroids and/or anticonvulsants for at least 14 days prior to first dose of study treatment, and their disease is asymptomatic and radiographically stable for at least 28 days prior to randomization by repeat imaging (repeat imaging should be performed during study screening)
21. Have had major surgery within 28 days prior to randomization
22. Have had wide-field radiotherapy ≤4 weeks (defined as involving ≥25% of the bone marrow), or limited field radiation for palliation ≤1 week prior to randomization. Patients must also have recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia)
23. Have a serious cardiac condition, such as
    a. congestive heart failure
    b. New York Heart Association Class III/IV heart disease
    c. unstable angina pectoris
    d. myocardial infarction within the last 3 months
    e. valvulopathy that is severe or moderate, or deemed clinically significant
    f. arrhythmias that are symptomatic or require treatment (not including patients with rate-controlled atrial fibrillation)
    g. cerebrovascular accident (stroke) within the last 3 months
    h. a mean QT interval corrected for heart rate of ≥470 msec on screening ECG, as calculated using the Fridericia's formula at several consecutive days of assessment
    i. baseline bradycardia with resting heart rate <60 beats per minute at several consecutive days of assessment
24. Have serious preexisting medical conditions 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], pre-existing medical condition of ILD/pneumonitis, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or

ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhea).

25. 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
26. Have received an autologous or allogeneic stem cell transplant
27. Have active bacterial or fungal infection, or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). Screening is not required for enrollment
28. Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 180 days after the last dose of study intervention
29. Have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents (for example, denosumab) <7 days prior to randomization
30. Known allergic reaction against any of the components of the study treatment.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized to a study treatment due to inability to complete or meet the criteria for participation (Sections 5.1 and 5.2) within the 28-day baseline screening period. Patients who are determined to be screen failures can be rescreened at an interval of ≥1 week. Patients may be rescreened up to 2 times after the initial screening. Each time rescreening is performed, the patient must sign a new ICF and will be assigned a new identification number. All required tests (see Schedule of Activities, Section 1.3) must be repeated for patients who are rescreened in a new 28-day baseline screening.

Repeating laboratory tests that did not meet eligibility criteria during the 28-day baseline screening period does not constitute rescreening. 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.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

	Arm A Imlunestrant	**Arm B** Investigator's Choice Endocrine Therapy		**Arm C** Imlunestrant + Abemaciclib	
Treatment	Imlunestrant	Fulvestrant	Exemestane	Imlunestrant	Abemaciclib
Dose	400 mg	500 mg	25 mg	400 mg	150 mg
Schedule	QD in 28-day continuous cycles	500 mg on C1D1 and C1D15 and then on Day 1 of a 28-day cycle starting at Cycle 2	QD in 28-day continuous cycles	QD in 28-day continuous cycles	BID in 28-day continuous cycles
Route	Oral	Intramuscular injection of two 250 mg injections	Oral	Oral	Oral
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Not authorized in EU	Authorized and used according to EU authorization

Abbreviations: BID = twice daily; C = cycle; D = day; QD = once daily.

Imlunestrant will be administered orally, 400 mg QD on Days 1 to 28 on a 28-day cycle. The imlunestrant doses will be administered at approximately the same times on each day. Patients should not consume any food at least 1 hour before and at least 2 hours after administration imlunestrant. Fasting requirements are also described in the patient diary.

The Investigator's Choice of Endocrine Therapy will be limited to fulvestrant or exemestane.

Fulvestrant will be administered 500 mg intramuscularly into the buttocks slowly as two 250 mg injections, one in each buttock on Days 1 and 15 of Cycle 1 of a 28-day cycle, then on Day 1 of Cycle 2 and beyond. However, 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 as one 250-mg injection. See local approved label for additional instructions.

Exemestane will be supplied as 25 mg and administered orally, 25 mg QD. See local approved label for additional instructions.

Abemaciclib will be administered orally, 150 mg BID on Days 1 to 28 on a 28-day cycle. The abemaciclib doses will be administered at approximately the same times on each day (see Section 6.1.4).

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 during treatment period. The 28-day cycle length should be maintained throughout the treatment phase regardless of dose interruptions. Patients will begin dosing assigned treatment on C1D1.

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

Patients with documented progressive disease (PD) as determined by the investigator may be allowed to continue study treatment if the patient is tolerating study drug and, in the opinion of the investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor. In addition to the permitted protocol windows (see Schedule of Activities, Section 1.3), a delay for a maximum of 7 days of a cycle start not due to an AE, but due to holiday, weekend, bad weather, or other unforeseen circumstances, will be permitted and not counted as a protocol deviation. Response assessments should remain on the original schedule (see Schedule of Activities, Section 1.3).

6.1.2. Arm A Imlunestrant: General Dosing Instructions

Each cycle will consist of 28 days. Imlunestrant will be given as 400 mg QD administered at approximately the same time on each day (refer to Section 6.1).

For imlunestrant administration, patients should follow the fasting guidance provided in the patient diary.

See Section 6.5 for concomitant medication guidance.

Patients randomized to imlunestrant treatment arms must keep a daily diary to record dosing compliance of oral study treatment, which will also be assessed at each clinic visit by means of a tablet count in the returned bottle(s). Late doses (that is, 4 or more hours after scheduled time) should be noted in the diary. Doses that are late by more than 6 hours should not be made up and recorded in the dosing diary as missed. Reasons should be recorded for any missed dose. Vomiting after dosing should be noted in the diary, and a vomited dose should not be re-dosed or replaced. Assessment of treatment compliance is described in Section 6.4.

Effects of imlunestrant on coagulation in humans are unknown. In rats, imlunestrant produced minimal to mild decreases in platelets and increases in prothrombin time that were partially to fully reversible. Thus, patients undergoing major surgical procedures should have imlunestrant held at least 3 days prior and 3 days post procedure; the Sponsor should be notified of the planned procedure and planned dose hold.

6.1.3. Arm B Investigator's Choice of Endocrine Therapy of Fulvestrant or Exemestane: General Dosing Instructions

Patients randomized to Arm B will begin dosing with investigator's choice of either fulvestrant or exemestane on C1D1, as outlined above in Section 6.1. Refer to local prescribing information for

additional administration details. Handling and administration of fulvestrant or exemestane should be in accordance with instructions per locally approved labelling or institutional standards.

6.1.4. Arm C Imlunestrant + Abemaciclib: General Dosing Instructions

Each cycle will consist of 28 days. Abemaciclib will be given at a starting dose of 150 mg BID and 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.

See Section 6.5 for concomitant medication guidance.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study interventions.
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 (that is, 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.

6.2.1. Arm A Preparation/Handling/Storage: Imlunestrant

Imlunestrant will be provided as tablets for oral administration and should be stored according to the product label, and not opened, crushed, or dissolved. Investigators should instruct patients to store the study drug in the original package and in a location inaccessible to children.

6.2.2. Arm B Preparation/Handling/Storage: Investigator's Choice of Endocrine Therapy of fulvestrant or exemestane

Preparation, storage, and handling for fulvestrant or exemestane will be according to instructions provided in the local label for the individual product.

6.2.3. Arm C Preparation/Handling/Storage: Imlunestrant + Abemaciclib

Abemaciclib will be provided as tablets for oral administration and should be stored according to the product label, and not crushed or dissolved. Investigators should instruct patients to store the study drug in the original package and in a location inaccessible to children.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a randomized, open-label study. The route of administration for the anti-cancer agents in the study justifies an open-label design. 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 the treatment arm. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Sites will be prompted to enter the specific Arm B ET of choice at time of randomization until the enrollment to Arm B is stopped. Each participant in this study will be aware of his or her own assigned treatment group. At each investigative site, all staff involved in treating and caring for study participants will have full knowledge of treatment assignments for the participants under their care.

In order to maintain the scientific integrity of the trial, access to study data will be strictly controlled prior to the interim and final analyses. Access to the EDC will be limited to those who require this information for their role and all access will be documented.

For the accumulated aggregate database to which Sponsor statisticians (or those of its designee) have access, treatment assignment, and other parameters that can disclose treatment assignment will be scrambled or masked. Therefore, the Sponsor and all investigative sites will remain blinded to treatment group assignments for the aggregate database until the database lock for the final analysis. Scrambled treatment assignments will be used in the reporting database until the study reaches its final analysis or the study is determined to be positive or futile by the DMC. During this time, analyses using unblinded treatment codes will be performed only at the interim analysis points specified in the protocol/SAP.

Participants will be randomized 1:1:1 between the 3 treatment arms, of either imlunestrant (Arm A), Investigator's Choice Endocrine Therapy (Arm B), or imlunestrant plus abemaciclib (Arm C), using the following stratification factors:

- previous treatment with any CDK4/6 inhibitor (yes versus no)
- presence of visceral metastases (yes versus no); visceral includes lung, liver, brain, pleural, and peritoneal involvement, and
- region (East Asia versus North America/Western Europe versus Others).

Arm C was added to the study (amendment a) after first patient visit for Arms A and B. Randomization of participants will continue in Arms A and B (1:1) until amendment a is approved and implemented, at which point participants will be randomized 1:1:1 (A:B:C) until the target enrollment for arms A and B (a total number of approximately 640 participants) is met.

Interim analyses for safety and efficacy will be conducted under the guidance of an independent DMC. The DMC will consist of at least 3 members, including at least 1 clinician and 1 statistician. The DMC will communicate any recommendations based on interim analysis to the Sponsor Senior Management Designee (SMD). If necessary, the SMD may form an Internal Review Committee (IRC) to review and act upon the recommendations of the DMC. Details will be specified in a separate DMC charter.

For those safety and efficacy 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 correct treatment assignments. At the request of the Sponsor, the SAC may provide pooled summary reports of the data to the Sponsor (for example, a summary of AEs across the study). These reports will not include treatment arms.

6.4. Study Intervention Compliance

Treatment compliance information for study treatment will be collected through patient dosing diaries and/or solid oral dosage unit counts at each visit, with the number of dosage units taken relative to the number expected to be taken summarized for each cycle. The patient must take ≥80% of the planned doses for study treatment in a cycle to be deemed compliant. Dose suspensions or delays may occur and will not result in a patient being considered as noncompliant. A patient may be considered noncompliant if judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study treatment in a cycle. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study and after the last dose of study treatment at the short-term follow-up Visit (See Schedule of Activities, Section 1.3) must be recorded in the eCRF and should be updated throughout the patient's participation in the study along with

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

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

Medications not permitted (All Arms)

Anticancer therapies for cancer (including ET, chemotherapy, immunotherapy) will not be permitted while patients are on study treatment. Use of megestrol acetate as an appetite stimulant is not permitted.

Strong inducers of CYP3A4 should also be avoided in patients receiving exemestane on-study.

Imlunestrant Guidance

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

CYP Substrates

In vitro assays indicated that imlunestrant is a time-dependent inhibitor of CYP2C8, CYP2C9, CYP2C19, and CYP3A. Imlunestrant is also predicted to be a clinically relevant reversible inhibitor of CYP2B6, CYP2C19, CYP2C8, CYP2C9, and CYP2D6. As a result, caution should be used with concomitant medications that are sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, or substrates of these CYPs with a narrow therapeutic index. A week of washout time following imlunestrant treatment is advised before

starting sensitive substrates of CYP2C8, CYP2C9, CYP2C19, and CYP3A (Section 10.11 Appendix 11, Section 10.12 Appendix 12, and Section 10.13 Appendix 13).

UGT1A1, P-gp and BCRP

According to preclinical studies, UGT1A1 is involved in the metabolism of imlunestrant. As a precaution, strong inducers and inhibitors of UGT1A1 should be avoided (Section 10.14 Appendix 14).

Due to limitations of in vitro assessments, the impact of imlunestrant as an inhibitor to P-gp and the Breast Cancer Resistance Protein (BCRP) in the gut wall cannot be ruled out. Therefore, caution should be exercised when co-administrating imlunestrant with narrow therapeutic index substrates of P-gp and BCRP (i.e. digoxin).

Consult the IB for additional information.

Abemaciclib Guidance

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

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 11, Section 10.11). 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 abemaciclib 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 abemaciclib for the duration of the CYP3A inhibitor medication.

Upon discontinuation of the strong CYP3A inhibitor, the dose of abemaciclib 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 abemaciclib dose requires review and approval from the Sponsor CRP/CRS.

Inducers of CYP3A should be substituted or avoided if possible (Appendix 11, Section 10.11). Coadministration with a CYP3A inducer ≥28 days must be discussed with the Sponsor CRP/CRS.

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.

6.5.1. Palliative Medicine and Supportive Care

Patients should receive full supportive care to maximize quality of life. Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Sponsor CRP. Use of any supportive care therapy should be reported in the eCRFs.

Palliative radiation therapy is permitted after discussion with and agreement of the Sponsor CRP/CRS or designee for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Such areas must not be an identified target lesion and must not constitute progressive disease or 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.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the CRF.

The use of granulocyte-colony stimulating factor is permitted at the discretion of the investigator based on ASCO (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2009) guidelines.

If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2008). Prophylactic antibiotic treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

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, replace a bisphosphonate with denosumab) while on study treatment. However, exceptional cases without evidence of PD may be considered in consultation with the Lilly CRP. These exceptional cases will not incur a protocol deviation.

6.5.2. Supportive Management for Diarrhea

Patients should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (for example, loperamide) and notify the investigator or site personnel for further instructions and appropriate follow-up.

- Patients should also be encouraged to drink fluids (that is, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- Follow dose modification guidance for imlunestrant (Section 6.6.1) and/or abemaciclib (Section 6.6.3), including dose suspension and/or reduction as appropriate.
- For severe cases of diarrhea, or any diarrhea associated with severe 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.

6.5.3. Photosensitivity

Based on an in vitro study, exposure to imlunestrant may result in photosensitivity. Patients are advised to avoid direct sun exposure and the use of tanning beds during study administrations period and at least 5 days after the last dose. If patients must be exposed to the sun, they should be advised to wear sunscreen, appropriate sun-blocking clothing, and sunglasses.

6.6. Dose Modification

General Considerations for Dose Delays.

In addition to the permitted protocol windows (see Schedule of Activities, Section 1.3), treatment cycles may be delayed up to 7 days due to holidays, weekends, bad weather, or other unforeseen circumstances and will not be deemed a protocol violation.

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

When a study drug is delayed, if possible and appropriate, patients should resume study treatment within 1 treatment cycle and, if not possible, then every effort should be made to start on the first day of the next dosing cycle. In rare circumstances, a delay of >28 days may be permitted before permanent treatment discontinuation, as long as the patient has clinical benefit without objective disease progression and is recovering from the toxicity. Such circumstances must be discussed with the Sponsor CRP/CRS. All dose modifications should be documented, including the approach taken and a clear rationale for the need for modification.

Dose Modifications for Imlunestrant

Management of some adverse reactions may require dose interruption and/or dose reduction. If dose reduction is necessary, decrease the dose by 200 mg. Discontinue imlunestrant for patients unable to tolerate 200 mg QD. In the event that imlunestrant must be discontinued, a participant may continue to receive abemaciclib (Arm C only).

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

Table 1: Imlunestrant Dose Reduction Guidelines

Dose Adjustment	Oral Dose Imlunestrant	Frequency
0	400 mg	QD
1	200 mg	QD

Abbreviation: QD = once daily.

6.6.1. Imlunestrant Dose Adjustments for Treatment-Emergent, Related*, and Clinically Significant Adverse Events

Treatment-emergent laboratory abnormalities of neutrophil count decreased and/or ALT/AST increased, regardless of clinical significance, must follow the dose adjustment table below.

*Related means there is a reasonable causal relationship with imlunestrant.

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at ≤Grade 2	Not required
	Grade 4 or Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at ≤Grade 2	Resume at next lower dose level
If Patient Requires Administration of Blood Cell Growth Factors	Regardless of severity	Dose **MUST** be suspended 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, second dose reduction not required)
Febrile neutropenia	Regardless of severity	Dose **MUST** be suspended until toxicity resolves	Resume at next lower dose level
Nonhematologic toxicity (except diarrhea, alopecia, and hepatotoxicity)[a]	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1	Not required
	Grade 3 or 4 (except non-hepatic asymptomatic laboratory changes)	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1	Resume at next lower dose level
Hepatotoxicity	AST/ALT >ULN - 5.0×ULN	Not required	
	Persistent or Recurrent: AST/ALT >3.0-5.0×ULN	Dose **MUST** be suspended until toxicity resolves to baseline or to >ULN-3.0×ULN	Not required

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
	AST/ALT >5.0-20×ULN **Or** ALT or AST ≥ 3 × baseline (if ALT or AST ≥ 1.5 × ULN at baseline) or AST/ALT >8 × ULN (whichever is the lower threshold)	Dose **MUST** be suspended until toxicity resolves to baseline or to ALT/AST>ULN - 3.0×ULN	Resume at next lower dose level
	AST/ALT >20.0×ULN **Or** ALT or AST ≥ 3 × ULN concurrent with TBL ≥ 2 × ULN (if ALT or AST < 1.5 × ULN at baseline), in the absence of cholestasis **Or** ALT or AST ≥ 2 × baseline concurrent with TBL ≥ 2 × ULN (if ALT or AST ≥ 1.5 × ULN at baseline), in the absence of cholestasis	Discontinue imlunestrant	
Diarrhea	Grade 1	Not required	
	Grade 2 that does not resolve with maximal supportive measures within 24 hours to ≤Grade 1	Suspend until toxicity resolves to ≤Grade 1	Not required
	Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures. Requires hospitalization or Grade 3 or 4	Suspend until toxicity resolves to ≤Grade 1	Resume at next lower dose level
Bloody diarrhea	Any grade	Dose **MUST** be suspended until bloody diarrhea resolves and diarrhea resolves to Grade ≤1	Resume at next lower dose level

Abbreviations: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] Events of diarrhea and hepatotoxicity should follow corresponding guidance listed in the table.

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

hematological toxicity, the investigator may consider resuming the participant on the same drug dose should the participant satisfy the following conditions:

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

6.6.2. Dose Modifications for Endocrine Therapy of Investigator's Choice

Dose adjustments for control arm ET of exemestane are not allowed.

Dose adjustments for control arm ET of fulvestrant will be determined by the investigator in accordance with the approved product labels. 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.

Dose suspensions ≥28 days must be discussed with the Sponsor CRP/CRS.

6.6.3. Dose Modifications for Abemaciclib

Management of some adverse reactions may require dose interruption and/or dose reduction. If dose reduction is necessary, decrease the dose by 50 mg at a time. Discontinue abemaciclib for patients unable to tolerate 50 mg BID. In the event that abemaciclib must be discontinued, a patient may continue to receive imlunestrant.

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

Recommended Dose Reduction Guidelines for Abemaciclib

Dose Adjustment	Abemaciclib Dose	Frequency
Starting dose	150 mg	BID
First dose reduction	100 mg	BID
Second dose reduction	50 mg	BID

Abbreviation: BID = twice daily.

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

Abemaciclib Dose Adjustments for Treatment-Emergent, Related Adverse Events

Toxicity Type	Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 1 or 2	Not required	
	Grade 3	Suspend until toxicity resolves to ≤Grade 2	Not required
	Grade 4 or recurrent Grade 3	Suspend until toxicity resolves to ≤Grade 2	Resume at next lower dose level
If Patient Requires Administration of Blood Cell Growth Factors Additional guidance for use of growth factors is in Section 6.5.1.	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, 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. 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 6.5.2.	Grade 1	Not required	
	Grade 2 that does not resolve with maximal supportive measures within 24 hours to ≤Grade 1	Suspend until toxicity resolves to ≤Grade 1	Not required
	Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures. Requires hospitalization or Grade 3 or 4	Suspend until toxicity resolves to ≤Grade 1	Resume at next lower dose level

Toxicity Type	Severity	Dose Suspension	Dose Reduction
ALT/AST Increased See Section 8.2.2.1 for additional guidance for hepatic monitoring.	>ULN-5.0×ULN or 1.5-5.0 × baseline (if baseline ≥1.5×ULN)	Not required	
	Persistent or recurrent >3.0-5.0×ULN (or × baseline if baseline ≥1.5×ULN), or >5.0-20.0×ULN (or × baseline if baseline ≥1.5×ULN)	Suspend until toxicity resolves to baseline or >ULN-3.0×ULN	Resume at next lower dose level
	>3.0×ULN (or × baseline if baseline ≥1.5×ULN)with total bilirubin >2×ULN, in the absence of cholestasis, or >20.0×ULN (or × baseline if baseline ≥1.5×ULN)	Discontinue abemaciclib	
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 Grade ≤1	Resume at next lower dose level
	Grade 3 or 4	Discontinue abemaciclib	

Abbreviations: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ILD = interstitial lung disease; ULN = upper limit of normal; 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 the next 8 weeks (as measured from the stop date of the first event. As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of the same Grade 3 hematological toxicity, the investigator may consider resuming the participant on the same drug dose should the participant satisfy the following conditions:

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

6.6.4. Re-escalation Criteria

If an imlunestrant and/or abemaciclib dose is reduced for 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 patient tolerates a reduced dose of imlunestrant and/or abemaciclib for ≥2 weeks, then the dose may be re-escalated to a prior dose level, at the discretion of the investigator and after consultation with the Sponsor CRP/CRS. After re-escalation, subsequent dose adjustments should be based on the dose that the patient is currently receiving.

6.7. Intervention after the End of the Study

The end of the study is defined in Section 4.4. Investigators will continue to follow the SoA provided in Section 1.3 until notified by the Sponsor that the end of the study has occurred.

Study completion will occur following the final analysis of OS, as determined by the Sponsor.

6.7.1. Continued Access

Patients receiving study treatment and experiencing ongoing clinical benefit may continue to receive study treatment in the continued access period until 1 of the criteria for discontinuation is met (Section 7). The continued access period will apply to this study only if at least 1 patient is still receiving study intervention when study completion occurs. The Sponsor will notify investigators when the continued access period begins. The Sponsor may allow patients to enroll in a "rollover" protocol to provide long-term continued access for patients enrolled in this study.

The continued-access period will begin after study completion and ends at the end of the study (Section 4.4). The patient's continued access to study treatment will end when a criterion for discontinuation is met (Section 7). Continued-access follow-up will begin when the patient and the investigator agree to discontinue study treatment. Follow-up procedures will be performed as shown in the SoA (Section 1.3).

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

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

Investigators will perform any other standard procedures, and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Sponsor will not routinely collect the results of these assessments.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Participant Discontinuation/Withdrawal from Study Treatment

Patients will be discontinued from study treatment in the following circumstances:

- at any time at his or her own request
- at the request of his or her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study – See Section 8.3.2 regarding regulatory reporting requirements
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- if the participant is significantly noncompliant with study procedures and/or treatment
- disease progression. Exceptions for continuing study treatment beyond confirmed radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from study treatment, and the investigator and the Sponsor agree that continuing study treatment is in the patient's best interest, and
- unacceptable toxicity.

Participants who discontinued from the investigational product prematurely for any reason will remain in the study and have short-term and long-term follow-up procedures as outlined in the SoA, Section 1.3.

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 or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1.1. Discontinuation of Inadvertently Enrolled Participants

If the Sponsor or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a decision on whether or not the patient may remain on treatment will be made between the Sponsor CRP/CRS and the investigator. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study treatment. Safety follow-up should be performed as outlined in Section 1.3 (Schedule of

Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events, Serious Adverse Events, and Product Complaints) of the protocol.

7.2. Discontinuation from the Study

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for survival. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Patients will be discontinued from the study in the following circumstances:

- the Sponsor determines that participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- the investigator decides the patient should be discontinued from the study
- the patient requests to be withdrawn from the study, and
- the study has been completed.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula (QTcF)) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the electrocardiogram printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.3. Lost to Follow-Up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented, and the patient will not be considered lost to follow-up.

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

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SOA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Appendix 4 (Section 10.4) provides a list of the laboratory tests that will be performed for this study.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.
- Procedures conducted as part of the patient's routine clinical management (for example, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

8.1. Efficacy Assessments

8.1.1. Efficacy Assessments at Baseline and during Study Treatment

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

All patients must have baseline brain imaging. For patients without a history of brain metastases, either a brain CT or brain MRI is required. Contrast is recommended. For patients without brain metastases as determined by baseline assessments, on-study brain imaging is not required, and sites may follow local/institutional standard of care guidelines.

For patients with treated brain metastases, contrast-enhanced brain MRI is preferred; however, if MRI contrast is contraindicated, then MRI (without contrast) or brain CT (recommended with

contrast) is acceptable. Patients with a history of brain metastases must have imaging should be repeated at the RECIST response assessment intervals outlined in the Schedule of Activities (Section 1.3).

For all patients, bone scintigraphy will be performed locally at baseline and repeated per the Study Schedule (Section 1.3). In addition, bone scans should be repeated if a CR in target disease is identified or progression in bone is suspected. For patients with new lesions identified by post-baseline bone scintigraphy, targeted assessment by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings.

For only those patients with RECIST non-measurable bone-only disease, for any lesions identified on bone scintigraphy at baseline that are not visible on the chest, abdomen, and 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 at baseline, per the Study Schedule (Section 1.3), and within 14 days of clinical progression.

For patients with locoregionally recurrent breast cancer not amenable to curative treatment, MRI scan of the breast will be performed at baseline, per the Study Schedule (Section 1.3), and within 14 days of clinical progression.

For patients with visible tumor (such as skin lesions), photography will be performed at baseline and each photographic image of the tumor should include a ruler. Photography should be performed at baseline and then per the Study Schedule (Section 1.3) and within 14 days of progression. Photographic images may be taken more frequently based upon the discretion of the investigator or following the identification of new skin lesions post-baseline.

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

8.1.2. Efficacy Assessments during Post-discontinuation Follow-Up

Post-discontinuation follow-up during the study period will be conducted as described in the SoA (Section 1.3). For those patients who are randomized and never receive study treatment or those who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response approximately every 8 weeks for the first 12 months with the first assessment relative to Cycle 1 Day 1 and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, death, start of a new anticancer therapy or study completion. In addition, anticancer therapies initiated after study treatment discontinuation will be collected during this follow-up period.

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

Tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3).

8.1.3. Primary Efficacy Measure

Response Evaluation Criteria in Solid Tumors v1.1 (Eisenhauer et al. 2009; Section 10.3 Appendix 3) will be applied as the primary criteria for assessment of tumor response and date of tumor progression. The method of tumor assessment used at baseline must be used consistently throughout the study. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Sponsor or its designee will collect and store all tumor assessment images on all randomized participants throughout the study to permit a blinded independent central review of patient scans. Please see the Site Imaging Manual for guidelines on how the various imaging studies should be performed.

The PFS time is measured from the date of randomization to the date of first objective progression or the date of death due to any cause, whichever is earlier. For those patients with nonmeasurable bone-only disease (refer to Inclusion Criterion [8]), objective progression will be established if at least 1 of the following criteria is met:

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

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 "new" bone lesions may be simply healing or flare of preexisting lesions). 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 9.4.3 for definitions of the efficacy endpoints.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

For each patient, ECGs, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3). Results from any clinical laboratory test analyzed (refer to Section 10.4 Appendix 4) will be provided to investigative sites by the Sponsor or its designee.

Refer to Section 8.3 for details on the recording of AEs.

8.2.1. Electrocardiograms

Local ECG's (no replicates required) should be obtained. Time points for ECG collection on-study are located in Section 1.3.2.

8.2.2. Clinical Safety Laboratory Assessments

See Appendix 4 (Section 10.4) for the list of clinical laboratory tests to be performed and see the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

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

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 4 (Section 10.4), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased) and it is known to be related to a disease diagnosis (for example, hypertension, neutropenia), this should be reported in the CRF as an AE. Do not enter the test abnormality; enter the disease diagnosis or categorical term. If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then the event(s) must be reported in the CRF as AEs.

8.2.2.1. Hepatic Safety Monitoring

Liver testing (Section 10.9 Appendix 9), including ALT, AST, alkaline phosphatase, TBL, direct bilirubin, gamma-glutamyltransferase, and creatine phosphokinase, should be repeated (local testing acceptable) within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

In participants with baseline ALT or AST <1.5 ULN

- Elevation of serum ALT or AST to ≥5× ULN
- The combination of elevated ALT or AST ≥3× ULN and elevated TBL ≥2× ULN

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

- Elevated ALT or AST ≥3× baseline
- The combination of elevated ALT or AST ≥2× baseline and elevated TBL ≥2× ULN

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

Based on the patient's history and initial evaluation results, further testing should be considered, in consultation with the Sponsor-designated medical monitor, including tests for hepatitis D

virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, and/or a liver biopsy.

For patients that meet the criteria above, whenever possible and as clinically appropriate, continue monitoring after discontinuation of imlunestrant until values are back to baseline.

Additional Hepatic Safety Collection

Additional safety data outlined in Section 10.9 Appendix 9 should be collected via the CRF if 1 or more of the following conditions occur:

In participants with baseline ALT or AST <1.5 ULN

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

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

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

In all study participants

- discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- occurrence of a hepatic event considered to be a SAE.

8.2.3. Safety Surveillance

The Sponsor has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with expectations of regulatory agencies. This includes processes with clearly described roles and responsibilities that are owned by the Sponsor's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (that is, review of cumulative SAEs and other important safety information) by designated cross-functional teams in a timely manner at predefined intervals or on an ad-hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs, as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program are reviewed on a regular basis and that important new safety information, such as the need for protocol modification or other relevant safety-related material, is identified and communicated to regulators and investigators appropriately and in a timely fashion. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any SARs are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing reports of SUSARs is created and distributed to investigators on a twice-yearly basis. Any

significant potential risk/safety concerns that are being monitored, as well as any results being reported in other periodic reports for the compound, SAC decisions, and other significant safety data (for example, nonclinical, clinical findings, and removal of SARs) are included in the report.

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. Abemaciclib dose adjustment should follow the protocol guidance for non-hematological toxicities in Section 6.6.3.

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 particular patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known.

Monitor participants for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate. Refer to Section 6.6.3 for guidance on dose adjustments of abemaciclib 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 6.6.3 for guidance on dose adjustments or discontinuation of abemaciclib for patients with ILD/pneumonitis.

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

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting the Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

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

Abnormal laboratory values should ONLY be reported as an AE if they are clinically relevant (See Section 10.6, Appendix 6).

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to the Sponsor or its designee via CRF, clarifying if possible the circumstances leading to any dosage modifications, or discontinuations of treatment.

The definitions of the following events can be found in Section 10.6, Appendix 6:

- Adverse events
- Serious adverse events, and
- Product complaints.

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 study treatment.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.6 Appendix 6. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.6 Appendix 6.

Timing and Mechanism for Collecting Events

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to the Sponsor begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving imlunestrant, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE CRF.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. SAEs, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he or she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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

8.3.1. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3).

8.3.2. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.3. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.7 Appendix 7.
- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 10.7 Appendix 7.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8.3.4. Cardiovascular and Death Events

Events leading to the clinical outcome of death due to study disease that are part of the efficacy analyses for this study will not be reported to the Sponsor or its designee as SAEs unless the investigator believes the event may have been caused by the investigational product.

8.3.5. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention.

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

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the intervention so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.1 and Section 10.6 Appendix 6 of the protocol.

Time Period for Detecting Product Complaints

Product complaints that result in an adverse event will be detected, documented, and reported to the sponsor during all periods of the study in which the intervention is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to an intervention provided for the study, the investigator will promptly notify the sponsor.

Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the sponsor by a method designated by the sponsor.

Follow-up of Product Complaints

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

In the event of an overdose, the investigator should:

- Contact the Sponsor CRS/CRP immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
- Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

Refer to the IB of imlunestrant and/or abemaciclib for available information on the signs, symptoms, and treatment of overdose.

If an overdose of any control arm therapy is suspected, investigators should follow locally approved label recommendations and actions accordingly.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3.2), venous blood samples will be collected to determine the plasma concentrations of imlunestrant, abemaciclib, and its

metabolites LSN3106726 and LSN2839567. Concentrations of imlunestrant and abemaciclib and its metabolites in plasma samples will be quantified using validated assay methodology in a laboratory designated by the Sponsor. Blood samples may also be used for exploratory metabolism work of imlunestrant and abemaciclib as deemed appropriate by the Sponsor.

Samples may be removed or 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 sampling will be recorded in the sample requisition form.

Differences from the time specified in the protocol are not considered protocol deviations as long as samples are collected, and accurate dates and times are recorded in a timely manner on the appropriate forms.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last participant visit for the study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow. See Section 10.8 Appendix 8 for information regarding genetic research.

8.8. Biomarkers

This study will analyze biomarkers relevant to study treatment, mechanism of action of imlunestrant, the variable response to study drug(s), immune function, tumor microenvironment, replication stress, angiogenesis, and pathways associated with cancer. Biomarker research may be performed to address questions of relevance to drug disposition, target engagement, PD, variability of participant response (including safety), and clinical outcome. Samples collected enable examination of these questions through the measurement of biomolecules, including DNA, ribonucleic acid, proteins, lipids, and other cellular elements. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

Collection of samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- tumor tissue (preferably from the most recently obtained nonbone biopsy) must be obtained for patients *if available**. Tissue blocks are preferred, otherwise ~25 x 5 um unstained slides, with verification of at least 20% tumor content, should be provided. Patients who do not have adequate archival tumor tissue available may undergo a fresh tumor biopsy prior to treatment if it is considered safe to perform and with the patient's consent. (*If archival tissue is not available and a fresh tumor biopsy cannot be performed, the patient may still be eligible to enroll if all other eligibility criteria are met.)
- plasma at multiple time points as specified in SoA.

The pathology report accompanying archival tissue may also be requested. The pathology report must be coded with the patient's study subject number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. The Sponsor has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site upon request. Slides and tissue samples collected on-study will not be returned.

All samples will be coded with the participant study number. These samples and any data generated can only be linked to the participant's study number. Personal identification information that can directly identify a patient will not be included with the sample.

Samples will be retained at a facility selected by the Sponsor or its designee for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period 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 imlunestrant or after imlunestrant becomes commercially available.

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

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. 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 and 8.8.

8.9. Health Outcomes and Medical Resource Utilization

8.9.1. Patient-Reported Outcomes

Self-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 of the region and linguistically validated. Only patients that are literate in an available translation will complete the questionnaires. The device will use an alarm feature to remind the subject/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. Since no paper version of the questionnaires are provided, patients with religious objections to using electronic devices are not required to complete these activities

The patient-reported outcomes including pain, cancer-related symptoms, physical function, adverse effect of diarrhea, and other health-related quality of life (HRQoL) outcomes will be used to compare across three treatment arms and generate health utility data. See Section 1.3.1 for patient-reported outcome (PRO) SoA.

All baseline assessment PRO questionnaires will be administered electronically on C1D1 prior to extensive interaction with site staff and study drug administration with the exception of the EORTC QLQ IL19 (not administered on C1D1 due to overlapping questions with EORTC QLQ-C30) and PRO-CTCAE item for injection site pain and swelling. Subsequent assessments will be completed at home according to the SoA for patient reported outcomes (Section 1.3.1) to minimize the number of activities required during clinic visits, with the exception of the SFU visit. At the SFU visit, patients with complete the specified assessments on the patient's ePRO device on site, therefore patients will be asked to bring their device with them for the SFU visit. While individual patients may vary in their response time, data from prior research among patients with advanced cancers suggest that 20 items can be completed in an average of less than 4 minutes using an electronic device.

8.9.2. 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, validated, 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 in the past 7 days:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning), and
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact).

This assessment will be completed by patients on a handheld electronic device at home (at site on C1D1 and SFU visit) every 8 weeks per the SoA in Section 1.3.1. To minimize patient burden, this instrument will be administered on an alternating schedule with the EORTC IL 19 instrument due to overlapping items (physical function domain). Assessment completion time is typically 5-7 minutes.

8.9.3. EORTC IL19: Physical Function

The EORTC IL19 consists of 5 items that are identical to the physical functioning subscale (items 1-5) of the EORTC QLQ-C30. This assessment will be completed by patients at home on an electronic handheld device on an every 8-week schedule as described in Section 1.3.1. To

minimize patient burden, the EORTC IL 19 scale will be first administered on C2D1 and will be administered in an alternating schedule with the EORTC QLQ-C30 such that the 2 instruments are completed 4 weeks apart from each other.

8.9.4. EQ-5D-5L

Health status will be assessed using the EQ-5D-5L (Janssen et al. 2008). 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 imaginable health state) to 0 (worst imaginable health state) as of "today." 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, every 8 weeks, according to the schedule described in Section 1.3.1.

8.9.5. PGIS (Patient's Global Impression of Severity) - Cancer Symptoms

The PGIS-Cancer Symptoms is a single-item assessment whereby patients are asked to report the overall severity of their cancer-related symptoms in the past 7 days using a 5-level response scale ranging from "No Symptoms" to "Very Severe." This assessment will be completed by the patient on an electronic device every 4 weeks as per the schedule described in Section 1.3.1.

8.9.6. mBPI-sf

The mBPI-sf (Cleeland 1991) is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for patients to record the presence of pain in general, pain relief, and pain interference with function (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 ranged through 10 (*pain as bad as you can imagine* or *completely interferes*). The mBPI-sf recall period is 24 hours, and typical completion time for this instrument is less than 5 minutes. This pain instrument will be completed by the patient at home on an electronic PRO device provided every 4 weeks as per the schedule described in Section 1.3.1.

8.9.7. Worst Pain NRS

The Worst Pain NRS is a single-item, extracted from the mBPI-sf. This item is subject-administered with an 11-point horizontal scale anchored at 0 ("no pain") and 10 ("pain as bad as you can imagine"). The recall period is the last 24 hours and will be completed daily at home by the patient on an electronic PRO device provided. The daily assessments for worst pain NRS will be collected during the study period, started at C1D1 to capture the baseline pain data as per the schedule described in Section 1.3.1.

8.9.8. PRO-CTCAE Items for Diarrhea and Injection Site Pain and Swelling

The PRO-CTCAE is a PRO measurement system developed by the National Cancer Institute to collect symptomatic AEs from cancer patients enrolled in clinical trials (Basch et al. 2014;

Dueck et al. 2015). These items have been developed to assess symptomatic AEs from the patient perspective associated with cancer therapy, to complement the CTCAE data collected at the site level (Basch et al. 2014, Atkinson et al. 2016). The information from the PRO-CTCAE will be used strictly for the study objective and shall not be reviewed by the site nor used in AE reporting.

A single question from the PRO-CTCAE item library was selected to characterize diarrhea. The single-item PRO-CTCAE will be completed weekly by the patient via the electronic device provided as per the SoA described in Section 1.3.1.

A single question from the PRO-CTCAE item library was selected to characterize injection site pain and swelling if any, for the patients who receive fulvestrant IM injections. The single item PRO-CTCAE will be completed by the patient weekly for 2 weeks following each administration of fulvestrant injection as per the SoA described in section 1.3.1.

8.9.9. Medical Resource Utilization

Medical resource utilization will be collected in the eCRF by the investigator and study site personnel for all patients throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected will include hospitalization, emergency room visit, radiation, surgery, and analgesic use.

9. Statistical Considerations

9.1. Statistical Hypotheses

Hypothesis 1: the imlunestrant arm (Arm A) will provide a clinically meaningful increase in PFS over the Investigator's Choice Endocrine Therapy (Arm B) in patients with ER+, HER2- locally advanced or mBC previously treated with ET in the ITT population.

Hypothesis 2: the imlunestrant arm (Arm A) will provide a clinically meaningful increase in PFS over the Investigator's Choice Endocrine Therapy (Arm B) in patients with ER+, HER2- locally advanced or mBC previously treated with ET in the *ESR1*-mutation detected population.

Hypothesis 3: the imlunestrant plus abemaciclib (Arm C) will provide a clinically meaningful increase in PFS over the imlunestrant arm (Arm A) in patients with ER+, HER2- locally advanced or mBC previously treated with ET in the ITT population.

9.2. Sample Size Determination

Participants will be randomly assigned to Arm A, Arm B or Arm C in a 1:1:1 ratio until the target enrollment for arms A and B (a total number of approximately 640 participants) is reached.

Though Arm C was added to the study (amendment a) after first patient visit for Arms A and B, all arms will be closed at the same time. Randomization of participants will continue in Arms A and B (1:1) until amendment a is approved and implemented, at which point participants will be randomized 1:1:1 (A:B:C) until the target enrollment for arms A and B (a total number of approximately 640 participants) is reached.

To adjust for multiplicity and control the overall type I error rate at 0.025 (1-sided), the graphical approach (Maurer and Bretz 2013) will be used to test the 3 PFS hypotheses and the 3 OS hypotheses. Initially, the overall 1-sided alpha level of 0.025 will be split between PFS for Arm A versus Arm B in the ITT population (H_1) and PFS for Arm A versus Arm B in the *ESR1*-mutation detected population (H_2), with H_1 tested at the 1-sided alpha level of 0.005 and H_2 tested at the 1-sided alpha level of 0.02. No alpha level (alpha=0) is initially assigned to the PFS endpoint for Arm C versus Arm A in the ITT population (H_3) and OS endpoints. The full graph including the OS endpoints and further details about the graphical approach will be provided in the SAP.

As the overall alpha is initially split between H_1 and H_2, the study will be considered positive (for Arm A versus Arm B) if either PFS in the ITT population (H_1) or PFS in the *ESR1*-mutation detected population (H_2) is statistically significant. The power and associated sample sizes for H_1 and H_2 are based on the initial allocation of alpha. The analysis population for the first primary hypothesis (PFS for Arm A versus Arm B in the ITT population) is all participants randomized to Arm A and Arm B. The primary analysis of PFS for Arm A versus Arm B in the ITT population will be performed when approximately 480 investigator-assessed events have been observed (that is, a 25% censoring rate) in Arm A and Arm B. Assuming a PFS hazard ratio of 0.74, a total of 480 events yields at least 76% power to detect superiority of imlunestrant Arm A over Arm B with the 1-sided log-rank test at the initial significance level of 0.005. If H_1 can be tested at the full alpha level of 0.025 after recycling per the graphical approach, the same number of events can yield at least 91% power with the 1-sided log-rank test. The median PFS of Arm B

is assumed to be 4.3 months, and the hazard ratio of 0.74 amounts to an approximate 1.5-month improvement in median PFS under the assumption of exponential survival distribution. The assumed median PFS of Arm B is estimated based on an unpublished meta-analysis of historical controls.

The analysis population for the second primary hypothesis (PFS for Arm A versus Arm B in the *ESR1*-mutation detected population) is the *ESR1*-mutation detected subset in Arm A and Arm B. The primary analysis of PFS will be performed when approximately 192 investigator-assessed events have been observed in the *ESR1*-mutation detected subset. Assuming a PFS hazard ratio of 0.57, a total of 192 events yields approximately 97% power to detect superiority of Arm A over Arm B with the 1-sided log-rank test at the significance level of 0.02. Assuming the median PFS of Arm B in the subset is 3.6 months, the hazard ratio of 0.57 amounts to an approximate 2.7-month improvement in median PFS under the assumption of exponential survival distribution.

The power and sample size for H_3 is based on the 1-sided alpha level of 0.025 assuming that both H_1 and H_2 are rejected. The analysis population of the third primary hypothesis (PFS for Arm C versus Arm A in the ITT population) is the participants concurrently randomized to Arm A and Arm C. The primary analysis of PFS will be performed when approximately 248 investigator-assessed events have been observed in this analysis population. Assuming a PFS hazard ratio of 0.7, a total of 248 events yields at least 80% power to detect superiority of Arm C over Arm A with the 1-sided log-rank test at the significance level of 0.025. If the median PFS of Arm A is assumed to be 5.8 months (assuming the target HR for Arm A versus Arm B in the ITT population is met), the hazard ratio of 0.7 then amounts to an approximate 2.5-month improvement in median PFS under the assumption of exponential survival distribution.

Previous enrollment assumptions were based on hypothetical enrollment rates. Under current rates of 35-40 participants per month, it is estimated that a total number of 860 participants will be enrolled to this study. Specifically, approximately 320 participants will be enrolled in Arms A and B, respectively, and approximately 220 participants in Arm C. The analysis population for PFS between Arm A and Arm B in the ITT population is all approximately 640 participants randomized to Arm A and Arm B, and the analysis population for PFS between Arm C and Arm A in the ITT population is the approximately 440 participants concurrently randomized to Arm A and Arm C. More details about the enrollment assumptions will be provided in the SAP.

9.3. Populations for Analyses

Populations are defined as follows:

Population	Description
ITT	All participants randomly assigned to study treatment, regardless of whether they take any doses of study treatment, or if they took 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
Evaluable	The subset of participants from the ITT population from whom a valid result has been obtained. Defined in the specific sections if applicable

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of 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 SAP and the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

Continuous variables will be summarized using descriptive statistics (that is, number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

Efficacy analyses will be based on the ITT population, unless otherwise stated. Safety analyses will be based on the safety population.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.025, unless otherwise stated, and all CIs will be given at a 2-sided 95% level.

The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

A detailed description of patient disposition will be provided, 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 patients completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation).

9.4.2.2. Participant Characteristics

A summary of participants demographic, baseline disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be provided.

9.4.2.3. Concomitant Therapy

A summary of preferred names of concomitant medications by treatment arm by decreasing frequency will be reported.

9.4.2.4. Post-Study Treatment Therapy

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

9.4.2.5. Extent of Exposure

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

9.4.2.6. Treatment Compliance

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. Study treatment taken will be derived from the difference between the total number of tablets dispensed and returned over the course of the patient's treatment. Compliance will only be assessed for imlunestrant, exemestane, and abemaciclib.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

The primary endpoint is investigator-assessed PFS. PFS is defined as the time from randomization to the date of first documented progression of disease or death from any cause in the absence of disease progression using RECIST version 1.1. Participants known to be alive and without disease progression will be censored at the last known date of progression-free assessment. A detailed PFS event/censoring scheme is provided in the table below. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves. Median PFS and PFS rates at various time points with 95% CIs will be estimated for each arm. The comparison of PFS curves between treatment arms will be conducted by a stratified log-rank test as the primary analysis, stratified by the randomization strata. The treatment effect will be estimated by hazard ratio with its corresponding 95% CIs using the stratified Cox proportional hazard model with treatment as the only covariate, stratified by the randomization strata.

For the primary objective of PFS for Arm A versus Arm B in the ITT population, 1 interim PFS analysis is planned when approximately 192 investigator-assessed events have been observed to allow the trial to stop early due to futility, and the final analysis will be conducted when approximately 480 investigator-assessed events have been observed in the same population. Details about the interim analysis are provided in Section 9.5.

For the primary objective of PFS for Arm A versus Arm B in the *ESR1*-mutation detected population, the final analysis will be conducted when approximately 192 investigator-assessed events have been observed. The comparison of PFS curves between treatment arms will be conducted by a stratified log-rank test as the primary analysis, stratified by the randomization strata. The treatment effect will be estimated by hazard ratio with its corresponding 95% CIs using the stratified Cox proportional hazard model with treatment as the only covariate. Strata may be collapsed to reduce the number of strata for the primary analysis. More details will be provided in the SAP.

For the primary objective of PFS for Arm C versus Arm A in the ITT population, one interim PFS analysis will be conducted when approximately 100 events have been observed among the approximately 440 participants concurrently randomized to Arm A and Arm C. This interim analysis will allow the trial (Arm A versus Arm C comparison) to stop early due to futility. Details are provided in Section 9.5. The final analysis will be conducted when approximately 248 events have been observed among the participants concurrently randomized to both arms. The PFS between Arm C and Arm A will only be tested hierarchically based on the graphical approach. More details will be provided in the SAP.

Sensitivity analyses including PFS analyses using different censoring rules, using the full ITT population (all randomized participants to corresponding arms for Arm C versus Arm A comparison), using unstratified log-rank test and unstratified Cox model may also be performed at the time of the final PFS analysis. Further details about these sensitivity analyses will be described in the SAP.

PFS Censoring Scheme

Situation	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate tumor assessment, per RECIST 1.1 criteria, or date of randomization (whichever is later)
	Unless	
No baseline radiologic tumor assessment available	Censored	Date of randomization
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following randomization	Censored	Date of randomization
New systemic anticancer therapy and no tumor progression or death	Censored	Date of adequate tumor assessment, per RECIST 1.1 criteria, prior to start of new therapy or date of randomization (whichever is later)
Tumor progression or death documented immediately after 2 or more missing scan intervals following last adequate tumor assessment or randomization (whichever is later)	Censored	Date of last adequate tumor assessment prior to 2 or more missing scans, per RECIST 1.1 criteria, or date of randomization (whichever is later)

Abbreviations: PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

a Symptomatic deterioration (that is, symptomatic progression that is not radiologically confirmed per RECIST 1.1 criteria) will not be considered as tumor progression.

b Adequate tumor assessment per RECIST 1.1 criteria refers to an assessment with 1 of the following responses: CR, PR, SD, or PD.

c The 2-scan interval is counted from the date of last adequate tumor assessment to the date of next 2 scheduled tumor assessments plus 8 days (adjusted by tumor assessment window).

d If there are multiple dates associated with 1 assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise.

9.4.3.2. Key Secondary Analyses

Overall survival between Arm A and Arm B in the ITT population, OS between Arm A and Arm B in the *ESR1*-mutation detected population and OS between Arm C and Arm A in the ITT population are the key secondary endpoints. To maintain the family-wise type I error rate, OS endpoints will be tested hierarchically based on the graphical approach. The full details about the graphical approach including OS endpoints will be provided in the SAP. Other secondary endpoints will not be error controlled.

Overall survival (OS) 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 analysis, OS data will be censored on the last date the patient is known to be alive. OS curves, median OS, and OS rates at 1 year, 2 years, and 3 years with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. OS will be compared between treatment arms using a log-rank test, stratified by the same factors as PFS. The corresponding hazard ratio between treatment arms will be estimated using a stratified Cox regression model. The inferential analysis of OS will be based on the stratified analyses. Unstratified analyses will also be performed. For Arm A versus Arm B in the *ESR1*-mutation detected population, OS will be analyzed using the same methods as PFS.

The analysis of each OS endpoint will be conducted in the same analysis populations for PFS as defined in Section 9.4.3.1. Interim analyses for each OS endpoint are also planned. Further details about the interim analyses for OS will be provided in the SAP.

9.4.3.3. Other Secondary Analyses

All other secondary analyses will be conducted for each comparison (Arm A versus Arm B in the ITT and *ESR1*-mutation detected populations and Arm C versus Arm A in the ITT population) per the prespecified analysis populations.

Objective response rate (ORR) is defined as the number of participants who achieve a confirmed best overall response of CR or PR divided by the total number of participants randomized to the corresponding treatment arm. The ORR with 95% CIs will be summarized for each treatment arm and compared between treatment arms using the Cochran-Mantel-Haenszel test adjusting for the randomization strata. The analysis of ORR will be conducted in the ORR evaluable population, which is defined as all randomized participants who have measurable disease per RECIST v1.1 at baseline.

Clinical benefit rate (CBR) is defined as the number of participants who achieve a best overall response of CR, PR, or SD ≥24 weeks divided by the total number of participants randomized to the corresponding treatment arm. The CBR with 95% CIs will be summarized for each treatment arm and compared between treatment arms using the Cochran-Mantel-Haenszel test adjusting for the randomization strata.

Duration of response (DoR) is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. The DoR will be censored according to the same rules as PFS. Median DoR with 95% CI and curves for each treatment arm will be estimated using the Kaplan-Meier method. The analysis of DoR will be based on participants who achieve an objective response (CR or PR).

Progression-free survival by blinded independent review committee (BIRC) is defined the same way as the primary endpoint of PFS. For BIRC analysis, scans will be collected and reviewed in all randomized participants based on RECIST version 1.1. PFS as assessed by BIRC intends to evaluate the reliability of the treatment effect based on the investigator-assessed PFS. PFS as assessed by BIRC will be analyzed using the same methods as the investigator-assessed PFS. The evaluation for the potential bias in the investigator assessment will also be performed. Further details will be described in the SAP.

9.4.4. Patient-Reported Outcomes and Medical Resource Utilization

Time to sustained worsening of worst pain is defined from the randomization to the time of the first increase (≥2 points) in the weekly average of the worst pain score with confirmation in the next consecutive week. Time to sustained worsening of worst pain will be summarized for each arm by the Kaplan-Meier method and will be compared between the 2 arms using the stratified log-rank test.

Time to worsening of physical function is defined as the time from randomization to the first ≥10-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.

Frequency counts of hospitalizations, emergency room visits, radiation, surgery, transfusion, and analgesic use will be summarized descriptively for each arm.

Full censoring rules for these endpoints will be described in the SAP. All the analyses will be conducted for each comparison (Arm A versus Arm B in the ITT and the *ESR1*-mutation detected populations and Arm C versus Arm A in the ITT population) per the prespecified analysis populations. Further analysis details will be described in the SAP.

9.4.5. Safety Analyses

Safety analyses will be based on the safety population, including the summaries of the following:

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

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

PK parameters for imlunestrant in plasma (for example, clearance, volume of distribution) and inter-individual PK variability will be computed using nonlinear mixed-effect modeling implemented in NONMEM. Covariate effects, such as age, weight, sex, and creatinine clearance, on the PK parameters of LY3484356 in plasma will also be investigated.

Concentrations of abemaciclib and its metabolites, LSN3106726 and LSN2839567 may be compared to previously established population PK models.

Biomarker data collected in this study may be used in a population PK/pharmacodynamic model.

9.4.7. Other Analyses

9.4.7.1. Exploratory Analyses

All the exploratory analyses will be conducted for each comparison (Arm A versus Arm B in the ITT and the *ESR1*-mutation detected populations and Arm C versus Arm A in the ITT population) per the prespecified analysis populations, unless otherwise stated.

Time to progressive bone metastases is defined as the time from randomization to the date of earliest development of new bone metastases. Time to progressive bone metastases will be summarized for each treatment arm using the Kaplan-Meier method and will be compared between 2 arms using the log-rank test.

Time to first SRE is defined as the time from randomization to the first SRE event defined as either pathological fracture, spinal cord compression, radiation to the bone, or surgery to the bone. Time to first SRE will be summarized for each treatment arm using the Kaplan-Meier method and will be compared between 2 arms using the log-rank test.

Time to chemotherapy is defined as the time from randomization to the initiation of first post-discontinuation chemotherapy. TTC will be summarized for each treatment arm using the Kaplan-Meier method and will be compared between 2 arms using the log-rank test.

Chemotherapy-free survival is defined as the time from randomization to the initiation of first post-discontinuation chemotherapy or death, whichever is earlier. CFS will be summarized for each treatment arm using the Kaplan-Meier method and will be compared between 2 arms using the log-rank test.

Progression-free survival 2 is defined as the time from randomization to disease progression on the next line of treatment or death, whichever is earlier. PFS2 will be summarized for each treatment arm using the Kaplan-Meier method and will be compared between 2 arms using the log-rank test.

Time to worsening of ECOG PS of ≥2 is defined as the time from randomization to the date when ECOG PS score of ≥2 was observed for the first time. Time to worsening of ECOG PS of ≥2 will be summarized for each treatment arm using the Kaplan-Meier method and will be compared between 2 arms using the log-rank test.

PFS and OS will be compared between Arm C and Arm B using the stratified log-rank test. The treatment effect will be estimated by hazard ratio with its corresponding 95% CIs using the stratified Cox proportional hazard model. The analysis population for Arm C versus Arm B is all concurrently randomized participants between two arms. Subgroup analyses will be conducted if deemed appropriate.

Further analysis details will be described in the SAP.

9.4.7.2. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for potential prognostic subgroup variables in each comparison, including but not limited to

- all baseline stratification factors
- *ESR1* mutation status (mutation detected versus mutation not detected) for the analyses in the ITT population
- measurable disease at baseline (yes versus no)
- age (<65 years versus ≥65 years)
- region (North America, Europe, Asia, and Other)
- race (Caucasian, Asian, and Other)
- PGR status (positive versus negative)
- baseline ECOG PS (0 versus 1), and
- number of organs involved (1 versus 2 versus 3+).

If a level of a factor consists of fewer than 5% of total number of events, analysis within that level may be omitted. Other subgroup analyses may be performed as deemed appropriate. Details are included in the SAP.

9.4.7.3. Biomarker Analyses

Biomarkers related to treatment, mechanism of action, and/or cancer will be measured and analyzed. Baseline *ESR1* mutation status (mutation detected versus mutation not detected) will be summarized. The association of biomarkers and clinical outcomes will be assessed via single-marker and/or multi-marker analysis.

9.5. Interim Analyses

9.5.1. Safety Interim Analyses

The DMC will monitor the overall safety of the study. An early safety analysis will be performed after approximately 100 participants have been randomized to all arms and had the opportunity to be treated for 1 cycle. The DMC will meet and review data approximately every 6 months thereafter. At the recommendation of the DMC, the frequency of safety interim analyses may be modified.

At each interim analysis, the DMC may recommend the trial continue without modifications, continue with specific modifications, or be stopped for safety concerns. There will be no prespecified rules for stopping the trial due to safety concerns. The DMC members will review unblinded safety data at each interim analysis. If a significant safety signal is identified, the DMC may recommend a protocol amendment, termination of enrollment, and/or termination of study treatment. The recommendations of the DMC will be communicated to the Sponsor SMD.

In the event that safety monitoring 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.

9.5.2. Efficacy Interim Analyses

One interim analysis is planned for the primary endpoint of PFS between Arm A and Arm B in the ITT population, when approximately 192 of the 480 events (40% information fraction) have been observed in the analysis population as defined in Section 9.2. The primary purpose of this interim is to allow the trial to stop early due to futility. The beta-spending function is determined by the gamma family. The DMC should recommend stopping the trial for futility if the hazard ratio is above 1.128. There is no intent to declare statistical significance for superior efficacy at this interim; therefore, there is no impact on the statistical significance levels for the final analysis.

For PFS between Arm A and Arm B in the *ESR1*-mutation detected population, if the target number of events in this subset has not been reached at the time of final PFS analysis in the ITT population, one interim analysis for efficacy may be conducted in the subset at the time of final analysis in the ITT population. The Lan-DeMets spending function (O'Brien-Fleming type) will be used to determine the boundaries at the interim and final analyses for PFS in the *ESR1*-mutation detected population.

Stopping Boundaries for Each Analysis between Arm A and Arm B in the ITT Population Based on the Initial Allocation of Alpha for Illustration

Analysis	Number of Events	Information Fraction	Critical P-value Boundary	Critical Hazard Ratio Boundary	Cumulative Type I Error Rate	Boundary Crossing Probabilities [a]		
						Hazard Ratio = 0.74	Hazard Ratio = 1	Hazard Ratio = 1.25
Interim	192	40%	NA	1.128	NA	0.002	0.203	0.757
Final	480	100%	0.005 (efficacy)	0.790	0.005	0.759	0.005	0

[a] Boundary crossing probabilities under different hazard ratio assumptions.

One interim analysis is planned for the primary endpoint of PFS between Arm C and Arm A when approximately 100 of the 248 events (40% information fraction) have been observed in the analysis population for this comparison as defined in Section 9.2. The purpose of the interim is to allow the trial comparison for Arm C versus Arm A to stop early due to futility. The beta-spending function is determined by the gamma family. Assuming the 1-sided alpha level of 0.025 will be used for testing this endpoint, the DMC should recommend stopping the trial (for Arm C versus Arm A) for futility if the hazard ratio is above 1.126. The boundary will be updated based on the actual number of observed events and the actual 1-sided alpha level that is used for this endpoint per the graphical approach. There is no intent to declare statistical significance for superior efficacy at this interim; therefore, there is no impact on the statistical significance levels for the final analysis.

Stopping Boundaries for Each Analysis between Arm C and Arm A in the ITT Population Based on the 1-sided Alpha Level of 0.025 for Illustration

Analysis	Number of Events	Information Fraction	Critical P-value Boundary	Critical Hazard Ratio Boundary	Cumulative Type I Error Rate	Boundary Crossing Probabilities [a]		
						Hazard Ratio = 0.7	Hazard Ratio = 1	Hazard Ratio = 1.25
Interim	100	40%	NA	1.126	NA	0.009	0.279	0.705
Final	248	100%	0.025 (efficacy)	0.779	0.025	0.794	0.027	0

[a] Boundary crossing probabilities under different hazard ratio assumptions.

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

An interim analysis may be collapsed with any other analyses including a final analysis if they are expected to occur within a similar timeframe (e.g., within approximately 2 month). Additionally, the final analysis of PFS between Arm A and Arm B in the ITT population may be collapsed with the final analysis in the *ESR1*-mutation detected population or the final analysis between Arm C and Arm A in the ITT population if they are expected to occur within a similar timeframe.

At the time of the final evaluation of PFS between Arm A and Arm B, the Sponsor will only have access to Arm A and Arm B data and will be blinded to Arm C if the final analysis between Arm A and Arm B is before the final analysis between Arm C and Arm A and is conducted by the Sponsor. Unblinding details are specified in a separate blinding and unblinding plan document.

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 GCP Guidelines, and
  - 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.
- 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
  - 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 or her representative will explain a description of the investigational drug, the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file. Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's 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 participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. 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's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Dissemination of Clinical Study Data

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete 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 pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

An EDC 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, eCOA data (questionnaires and scales) will be directly recorded by the patient, into an instrument (for example, an electronic device). 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 party (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 the central vendor's database system and 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.

10.1.7. Source Documents

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

10.1.8. Study Closure

Study site participation may be discontinued if the Sponsor or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.2. Appendix 2: Protocol JZLC ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework and office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

10.3. Appendix 3: Protocol JZLC RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

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

Measurable

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

- 10 mm by CT or MRI scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers), and
- 20 mm by chest X-ray.

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques, such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable).

- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

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

Nontarget Lesions

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

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

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment (except for the baseline bone scintigraphy, which may be obtained up to 45 days prior to the beginning of the treatment).

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

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

Clinical Lesions: clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

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

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

Ultrasound: ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

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

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

Cytology, Histology: these techniques can be used to differentiate between PRs and CR in rare cases if required by protocol (for example, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or

angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

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

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a CR or PR in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Nontarget Lesions

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

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

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

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

Evaluation of Best Overall Response

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

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs (when no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point). Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 2: Time Point Response: Patients with Target (± Nontarget) Disease

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

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

Table 3 is to be used when patients have *nonmeasurable* disease only.

Table 3: Time Point Response: Patients with Nontarget Disease Only

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

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease.
[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Reevaluation

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

Confirmatory Measurement/Duration of Response

Confirmation
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

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

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

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

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

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

Independent Review of Response and Progression

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

10.4. Appendix 4: Clinical Laboratory Tests

- The tests detailed below will be performed as indicated in the table below.
- If there is an abnormal laboratory value or abnormal value for a diagnostic or screening test (for example, blood pressure increased, neutrophils decreased) and it is associated to a diagnosis of an AE, then the AE should be entered in the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.
- Enrollment and treatment decisions may be based on local chemistry laboratory results, but a specimen must also be sent to central laboratory. Discrepancies between local and central laboratory results will not be considered protocol deviations.
- 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 each laboratory safety report.

Clinical Laboratory Tests	
Hematology	
Leukocytes (WBC)	Assayed by local laboratory
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Erythrocytes (RBC)	
Hemoglobin (HGB)	
Hematocrit (HCT)	
Platelets (PLT)	
Clinical Chemistry	
Alanine aminotransferase (ALT)	Assayed by Central laboratory
Albumin	
Alkaline phosphatase	
Aspartate aminotransferase (AST)	
Bilirubin, direct	
Bilirubin, total	
Blood urea nitrogen (BUN) or blood urea	
Calcium	
Creatinine	
Glucose (random)	
Potassium	
Protein	
Sodium	
Cystatin C (obtained as clinically indicated)[d]	

Coagulation	
PT/INR	Assayed by local laboratory
aPTT	
Fasting Lipid Panel - central laboratory	
Cholesterol	Assayed by central laboratory
High-density lipoproteins	
Low-density lipoproteins	
Triglycerides	
Hormone Testing (Female)	
Serum Pregnancy test: For Screening - local laboratory[a] for women of childbearing potential[b]	Evaluated by local laboratory
Follicle-stimulating hormone (FSH)[a, c]	
Estradiol[a, c]	Evaluated by local or investigator-designated laboratory

Abbreviations: aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

[a] Local or investigator-designated laboratory.

[b] Local regulations and/or institutional guidelines may require additional testing.

[c] FSH and Estradiol are obtained at screening for women <60 years of age if needed to verify menopausal status; and Estradiol is monitored on study for women receiving GnRH agonist for ovarian function suppression.

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

[d] See Section 8.2.4

10.5. Appendix 5: Creatinine Clearance Formula

Note: this formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

Cockcroft-Gault prediction of CrCl from serum creatinine (1976)

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine}\ \text{(mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ \text{(µmol/L)}}$$

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

10.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.6.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: an AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events 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 preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug–drug interaction. • Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.6.2. Definition of SAE

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

SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. Is a congenital anomaly/birth defect

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

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 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.

10.6.3. 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.

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

AE, SAE, and Product Complaint Recording

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

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

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

Assessment of Intensity

The investigator will use CTCAE version 5.0 (NCI 2018) to assign AE severity grades.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his or her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he or 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 or her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

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

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- 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.

10.6.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor 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, IRBs/IECs), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:
1. Premenarchal
2. Premenopausal female with at least 1 of the following:
   - Documented hysterectomy, or
   - documented bilateral salpingectomy, or
   - documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female is defined as, women with
   - 12 months of amenorrhea for women >60, with no need for FSH
   - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that induced amenorrhea). If fertility is unclear, then additional evaluation should be considered.

Contraception Guidance:

Patients with reproductive potential (that is, non-postmenopausal patients) are instructed to use highly effective contraceptive methods. The choice of the most effective and appropriate contraception method is up to the investigator's judgment after discussion with the patient, taking into account age, pregnancy, and other gyneco-obstetrical history, sexual activity, patients' preference, acceptance of the contraception method, and potential adherence.

In patients with breast cancer, the use of estrogen-based hormonal contraception (includes the hormonal IUDs) is contraindicated, and the effect of progestin-based hormonal contraception remains unclear.

The Clinical Trial Facilitation Group has defined highly effective methods of contraception.[1]

Highly effective methods include

- intrauterine device

- bilateral tubal occlusion
- vasectomized partner[2], and
- sexual abstinence[3].

Due to the possible risk of human teratogenicity/fetotoxicity, non-highly effective methods (such as double-barrier methods) of contraception are not allowed.

Local regulation/guidelines are to be followed with regard to highly effective birth control method, if more restrictive.

[1]Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. September 2020. Accessed September 22, 2021. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf.

[2]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[3]In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of 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 up 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 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 at >20 weeks gestational age) is always considered to be an SAE and 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 8.3.3. 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 intervention, follow the standard discontinuation process and continue directly to the follow-up phase.

10.8. Appendix 8: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Assessment of variable response may include evaluation of AEs or differences in efficacy. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to imlunestrant or breast cancer and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to study intervention and/or interventions of this drug class and indication. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Samples may also be used to determine the somatic or germline origin of tumor-associated genetic alterations.
- Samples will not be used to conduct unspecified disease or population genetic research either now or in the future.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to imlunestrant or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.
- Samples will be retained at a facility selected by the Sponsor or its designee for a maximum of 15 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. This retention period 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 imlunestrant or after imlunestrant become(s) commercially available.
- Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome and exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing

See Section 10.4, Appendix 4 and Section 8.2.2.1 for guidance on appropriate test selection.

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.

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

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

Hepatitis B core IgM antibody	CMV antibody
Hepatitis B core IgG antibody	CMV DNA[b]
HBV DNA[b]	Herpes simplex virus (HSV) testing:
Hepatis C virus (HCV) testing:	HSV (Type 1 and 2) antibody
HCV antibody	HSV (Type 1 and 2) DNA[b]
HCV RNA[b]	Liver Kidney Microsomal Type 1 (LKM-1) antibody
Hepatitis D virus (HDV) testing:	
HDV antibody	
Hepatitis E virus (HEV) testing:	
HEV IgG antibody	
HEV IgM antibody	
HEV RNA[b]	

Abbreviations: CRP = clinical research physician; CRS = clinical research scientist; DNA = deoxyribonucleic acid; Ig = immunoglobulin; INR = international normalized ratio.

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

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

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

10.10. Appendix 10: Country-specific Requirements

The country-specific addenda reflected in this appendix must be performed in each of the respective countries, in addition, to all procedures required by current version of Protocol J2J-OX-JZLC (JZLC) where applicable. The consolidation of these individual country-specific addenda into this appendix is to facilitate transition of this trial to the CTIS system under the new clinical trial regulation in Europe.

10.10.1. Belgium

This addendum will address feedback from the Federal Agency for Medicines and Health Products (FAMHP) in Belgium and the Ethics Committee (EC) regarding the request to amend the original EMBER-3 protocol.

The following table describes the changes being made to Protocol JZLC for participants in Belgium:

Protocol Section # and Name	**Description of Change**
1.3. Schedule of Activities 10.4. Appendix 10.4: Clinical Laboratory Tests	Revised to require FSH and estradiol testing during the on study treatment period. *Note: this revision was added to the global protocol in amendment (a).*
1.3. Schedule of Activities 10.4. Appendix 10.4: Clinical Laboratory Tests	Revised to require pregnancy testing during the study treatment period and at short-term follow-up.
5.1. Inclusion Criteria	Modified criteria 6 and 7 to specify that patients that receive fulvestrant should use highly effective methods of contraception for 2 years after the last dose. *Note: this revision was added to the global protocol in amendment (a).*
6.1.2. Arm A LY3484356: General Dosing Instructions	General dosing instructions Section 6.1.2 was revised to reflect the most up to date limitations of in vitro assessments and the potential impact of imlunestrant as an inhibitor to P-gP and the Breast Cancer Resistance Protein (BCRP). *Note: this revision was added to the global protocol in amendment (a).*

All additions have been identified by the use of <u>underline</u>, and deletions have been identified by ~~strikethrough~~.

Section 1.3. Schedule of Activities (Belgium)

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1		2–3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1	2	3–4	5 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Lab/ Diagnostic Tests	FSH and estradiol levels	X			X	X			Section 10.7 Appendix 7	• For Screening: local testing required only for women <60 years with amenorrhea for at least 12 months to confirm post-menopausal status • For on-study: Required every 3 months (± 5 days) only for women < 60 years
	Pregnancy Tests	X			X	X	X		Section 10.7 Appendix 7	• Local testing • For Screening: serum pregnancy test required for women of child-bearing potential • For On Study: local testing for women of child-bearing potential • For Short-Term Follow-Up: local testing for women of child-bearing potential

Abbreviation: FSH = follicular stimulating hormone.

[a] Short-term follow-up period begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days; the associated study procedures are performed once at the end of this period. Long-term follow-up period begins the day after short-term follow-up visit is completed and continues until the patient's death or overall study completion; the associated study procedures are performed approximately every 12 weeks (± 14 days) for the duration of this period beginning 12 weeks after the short-term follow-up visit.

Section 5.1. Inclusion Criteria

6. If female and postmenopausal status is due to ovarian suppression, participants must have a negative serum pregnancy test at baseline (within 14 days prior to enrollment) and agree to use highly effective, medically approved precautions to prevent pregnancy (see Section 10.7 Appendix 7) during the study and for 6 months (2 years for patients receiving fulvestrant) following the last dose of study treatment.

7. If male, must agree to use the following:

a. 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. highly effective methods of birth control and to not donate sperm during the study and for at least 6 months (2 years for patients receiving fulvestrant) following the last dose of study drug(s), or for the duration specified in country requirements, whichever is longer.

Section 6.1.2. Arm A LY3484356: General Dosing Instructions

Each cycle will consist of 28 days. LY3484356 will be given as 400 mg QD administered at approximately the same time on each day (refer to Section 6.1).

For LY3484356 administration, patients should follow the fasting guidance provided in the patient diary.

Because LY3484356 is metabolized by CYP3A4, patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products and avoid medications considered strong inducers and inhibitors of CYP3A and P-glycoprotein (P-gp) 2 weeks prior to and while on study due to the effect on CYP3A4 and/or P-gp.

Due to limitations of in vitro assessments, the impact of LY3484356 as an inhibitor to P-gP and the Breast Cancer Resistance Protein (BCRP) in the gut wall could not be ruled out. Therefore, caution should be exercised when co-administering LY3484356 with narrow therapeutic index substrates of P-gp and BCRP (i.e. digoxin).

Appendix 10.4: Clinical Laboratory Tests

Clinical Chemistry - central laboratory

Serum Concentrations of:

Alanine aminotransferase (ALT)
Albumin
Alkaline phosphatase
Aspartate aminotransferase (AST)
Bilirubin, direct
Bilirubin, total
Blood urea nitrogen (BUN) or blood urea
Calcium
Creatinine

Estradiol
Follicular Stimulating Hormone (FSH)
Glucose (random)
Potassium
Protein
Sodium
Pregnancy Test (for female patients of childbearing potential)
For Screening- local laboratory [a, b] Serum pregnancy test
On Study and Short-Term Follow-Up – local laboratory test [a,b]

Abbreviations: aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

a Local or investigator-designated laboratory.

b Local regulations and/or institutional guidelines may require additional testing.

10.10.2. Czech Republic

This addendum will address feedback from the Czech Republic regarding the request to amend the EMBER-3 protocol. The following table describes the changes being made to Protocol JZLC for participants in Czech Republic:

Protocol Section # and Name	Description of Change
1.3. Schedule of Activities	Added HIV and viral hepatitis screening and indicated that this screening will be conducted locally.
5.1. Inclusion Criteria	Adjusted hemoglobin laboratory value cutoff to ≥9 g/dL in criterion 10. *Note: this was added to the global protocol in amendment (b).*
5.2. Exclusion Criteria	Increased required interval since major surgery to 28 days in criterion 21. *Note: this was added to the global protocol in amendment (b).* Removed "screening is not required for enrollment" from criterion 27.

All additions have been identified by the use of underline, and deletions have been identified by ~~strikethrough~~.

Section 1.3 Schedule of Activities (Czech Republic)

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1 and 2		3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1, 3	2, 4	5	6 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Lab/Diagnostic Tests	HIV and viral hepatitis screening	X								• Local testing

Section 5.1 Inclusion Criteria

10. Have adequate organ function as defined in table below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥9~~8~~ g/dL

Note: transfusions to increase a patient's hemoglobin level 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.

Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte colony stimulating factor.

Section 5.2 Exclusion Criteria

21. Have had major surgery within 28~~14~~ days prior to randomization
27. Have active bacterial or fungal infection, or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). ~~Screening is not required for enrollment.~~

10.10.3. France

This addendum will address feedback from France regarding the request to amend the EMBER-3 protocol. The following table describes the changes being made to Protocol JZLC for participants in France:

Protocol Section # and Name	Description of Change
5.1. Inclusion Criteria	Modified criterion 3 to note that investigators must document in the patient records the basis for including participants that have not been treated with a CDK4/6 inhibitor prior to study enrollment, rather than treating with a CDK4/6 inhibitor.
7.1. Participant Discontinuation/Withdrawal from Study Treatment	Modified to discontinue, without exception, all patients that develop disease progression on study treatment.

All additions have been identified by the use of underline, and deletions have been identified by ~~strikethrough~~.

Section 5.1. Inclusion Criteria

3. Have locally advanced (not amenable to curative treatment by surgery) or metastatic disease and fulfill 1 of the following criteria below~~:~~. CDK4/6 inhibitors are a treatment option in these patients. Therefore, for patients who have not received treatment with a CDK4/6 inhibitor prior to enrollment into the trial, the investigator must document in the patient records the rationale for including them in this trial rather than treatment with a CDK4/6 inhibitor.
    a. relapsed with evidence of progression while on or within 12 months of completion of (neo)adjuvant AI, alone or in combination with a CDK4/6 inhibitor, with no treatment for advanced disease
    b. relapsed with evidence of progression >12 months from completion of (neo)adjuvant ET, with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor. Patients may not have received any other prior therapy (other than the aforementioned: AI, alone or in combination with a CDK4/6 inhibitor) in the advanced/metastatic setting
    c. presented de novo with metastatic disease, with subsequent progression on or after only 1 line of therapy with an AI, alone or in combination with a CDK4/6 inhibitor. Patients may not have received any other prior therapy (other than the aforementioned: AI, alone or in combination with a CDK4/6 inhibitor) in the advanced/metastatic setting.

Section 7.1. Participant Discontinuation/Withdrawal from Study Treatment

Patients will be discontinued from study treatment in the following circumstances:

- if the participant is significantly noncompliant with study procedures and/or treatment
- disease progression ~~Exceptions for continuing study treatment beyond confirmed radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from study treatment, and the investigator and the Sponsor agree that continuing study treatment is in the patient's best interest~~, and
- unacceptable toxicity.

10.10.4. Germany

This addendum will address feedback from Germany regarding the request to amend the EMBER-3 protocol. The following table describes the changes being made to Protocol JZLC for participants in Germany:

Protocol Section # and Name	**Description of Change**
1.3. Schedule of Activities	Addition of pregnancy test at the short-term follow-up visit. *Note: this was included in the global protocol with amendment (a).*
1.3. Schedule of Activities 5.2. Exclusion Criteria	Modified criterion 27 to require HIV screening test for enrollment and added procedure to Schedule of Activities.
5.1. Inclusion Criteria	Modified criteria 6 and 7 to specify that patients that receive fulvestrant should use highly effective methods of contraception for 2 years after the last dose. *Note: this was included in the global protocol with amendment (a).*
5.1. Inclusion Criteria	Modified criterion 11 to allow for an acceptable washout period for safety reasons.
7.1. Participant Discontinuation/Withdrawal from Study Treatment 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.1.3. Informed Consent Process	Removed references to the participant's "legally authorized representative".
10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information	Modified to specify that double barrier methods of contraception are not allowed. *Note: this was included in the global protocol with amendment (a), (b).*
10.10.1. Discontinuation of Inadvertently Enrolled Patients in the United Kingdom	Modified section to include Germany.
10.16. Appendix 16: Provisions for Changes in Study Conduct during Exceptional Circumstances	Modified to reflect submission of an addendum in Germany when implementing activities under exceptional circumstances.

All additions have been identified by the use of underline, and deletions have been identified by ~~strikethrough~~.

Section 1.3. Schedule of Activities (Germany)

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1		2–3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1	2	3–4	5 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Lab/Diagnostic Tests	Pregnancy test	X					X		Section 10.7 Appendix 7	• Local testing • For Screening: serum pregnancy test required for women of child-bearing potential • For on Study: per local regulations and/or institutional guidelines
	HIV and viral hepatitis screening	X								

Section 5.1. Inclusion Criteria

6. If female and postmenopausal status is due to ovarian suppression, participants must have a negative serum pregnancy test at baseline (within 14 days prior to enrollment) and agree to use highly effective, medically approved precautions to prevent pregnancy (see Section 10.7 Appendix 7) during the study and for 6 months (2 years for patients receiving fulvestrant) following the last dose of study treatment

7. If male, must agree to use the following:
    a. 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. highly effective methods of birth control and to not donate sperm during the study and for at least 6 months (2 years for patients receiving fulvestrant) following the last dose of study drug(s), or for the duration specified in country requirements, whichever is longer

11. Have discontinued previous therapies for cancer prior to receiving study drug, 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:
    a. for myelosuppressive agents (for example, CDK4/6 inhibitors): at least 21 days
    b. for nonmyelosuppressive agents (for example, Endocrine Therapy): 7 days or 5 half-lives, whichever is ~~shorter~~longer
    c. for investigational agents: 28 days or 5 half-lives, whichever is ~~shorter~~longer

Section 5.2. Exclusion Criteria

27. Have active bacterial or fungal infection, or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). Screening is ~~not~~ required for enrollment

Section 7.1. Participant Discontinuation/Withdrawal from Study Treatment

Patients will be discontinued from study treatment in the following circumstances:

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

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

The definitions of the following events can be found in Section 10.6, Appendix 6:

- Adverse events
- Serious adverse events, and
- Product complaints.

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient ~~and/or legal guardian~~ is the preferred method to inquire about AE occurrences.

Section 10.1.3. Informed Consent Process

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

Section 10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

~~If the highly effective contraceptive methods are contraindicated or strictly declined by the patient, or in the event of sexual activity of low frequency, a combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered an acceptable birth control method~~.

Due to the possible risk of human teratogenicity/fetotoxicity, double-barrier methods of contraception are not allowed.

Local regulation/guidelines are to be followed with regard to highly effective birth control method, if more restrictive.

Section 10.10.1. Discontinuation of Inadvertently Enrolled Patients in the United Kingdom and Germany

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

Section 10.16. Appendix 16: Provisions for Changes in Study Conduct during Exceptional Circumstances

Implementing changes under exceptional circumstances

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

After approval by local ERBs, 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 conditions in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records. For Germany, a country level addendum must be submitted.

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

10.10.5. Italy

This addendum will address feedback from Italy regarding the request to amend the EMBER-3 protocol. The following table describes the changes being made to Protocol JZLC for participants in Italy:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Expanded AE collection to include any SAE regardless of relationship to study treatment and AEs possibly related to study treatment or study procedure during the long-term follow-up period. *Note: the revision above was added to the global protocol in amendment (a).* Included coagulation assessments on Day 1 of Cycle 1 and Cycle 2.	To comply with feedback from the Italian Medicines Agency.
Section 5.1 Inclusion Criteria	Updated language in Criterion 5.	To align the definition of postmenopausal state with the 2014 Clinical Trial Facilitation and Coordination Group recommendations related to contraception and pregnancy testing in clinical trials.

All deletions have been identified by ~~strikethrough~~; all additions have been identified by the use of underscore.

Section 1.3 Schedule of Activities (Italy)

	Study Period	Baseline	Study Treatment (Cycle =28 days)				Post-discontinuation Follow-Up			
	Cycle	Screening	1		2–3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]		
	Visit	0	1	2	3–4	5 and Beyond (if Applicable)	801	802–8XX		
	Relative Day within a Cycle	≤28	Day 1	Day 15[c] (± 3)	Day 1 (± 3)	Day 1 (± 3)	Day 30 (± 7)	(± 14)		
Procedure Category	**Procedure**								**Protocol Reference**	**Instructions**
Adverse Event Collection/ CTCAE Grading		X	X		X	X	X	X	Section 8.3	• Collect continuously at every visit and throughout the study • CTCAE Version 5.0 • For long-term follow-up: ~~only~~ all SAEs ~~that are related to study drugs or protocol procedures~~ regardless of relationship to study treatment and adverse events possibly related to study treatment or study procedure will be collected • All adverse events possibly related to study drugs or protocol procedures should be followed until they resolve, are no longer considered to be possibly related, become stable or return to baseline, the patient starts a new therapy, the patient expires, or the patient becomes lost to follow-up. The frequency of evaluation is determined according to the judgment of the investigator
Lab/Diagnostic Tests	Coagulation	X	X		X				Section 10.4 Appendix 4	• Perform at baseline, Cycle 2 Day 1 (Visit 3), and as clinically indicated • Local testing

Section 5.1 Inclusion Criteria

5. If female, have a postmenopausal status due 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 due to surgical/natural menopause requires at least 1 of the following:
    a. prior bilateral oophorectomy
    b. age ≥60 years, amenorrheic for at least 12 months, in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression
    c. age <60 years, amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression), and FSH and estradiol levels in the postmenopausal range.

10.10.6. Spain

This addendum will address feedback from Spain regarding the request to amend the EMBER-3 protocol. The following table describes the change is being made to Protocol JZLC for participants in Spain:

Protocol Section # and Name	Description of Change
5.2. Exclusion Criteria	Updated criterion 15 to state the following, "Patients who have completed a prior exemestane treatment may not receive exemestane if they are randomized to the control arm".

All deletions have been identified by ~~strikethrough~~; all additions have been identified by the use of underscore.

Section 5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria applies:

> [15] Have received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, any investigational-ER-directed therapy (including SERDs and non-SERDs), any PI3K-, mTOR-, or AKT-inhibitor. Patients who have completed prior exemestane treatment may not receive exemestane if randomized to the control arm.

10.11. Appendix 11: Inducers and Strong Inhibitors of CYP3A

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

Strong Inducers of CYP3A
Aminoglutethimide
Apalutamide
Avasimibe
Carbamazepine
Enzalutamide
Fosphenytoin
Ivosidenib
Lumacaftor
Mitotane
Phenobarbital/phenobarbitone
Phenytoin
Rifabutin
Rifampicin
Rifapentine
St John's wort

Moderate Inducers of CYP3A
Almorexant
Bosentan
Cenobamate
Dabrafenib
Daclatasvir and asunaprevir and beclabuvir
Danshen
Efavirenz
Encorafenib
Etravirine
Faldaprevir and efavirenz
Genistein
Lersivirine
Lesinurad
Lopinavir (alone)
Lorlatinib
Modafinil
Nafcillin (intravenous)
Pentobarbital
Primidone
Telotristat ethyl
Thioridazine
Tipranavir and ritonavir
Tocilizumab

Strong Inhibitors of CYP3A
Boceprevir
Clarithromycin
Cobicistat
Conivaptan
Danoprevir and ritonavir
Diltiazem
Elvitegravir and ritonavir
Grapefruit juice
Idelalisib
Indinavir and ritonavir
Itraconazole
Ketoconazole
Lopinavir and ritonavir
Nefazodone
Nelfinavir
Posaconazole
Ribociclib
Ritonavir
Saquinavir and ritonavir
Telithromycin
Tipranavir and ritonavir
Viekira Pak
Voriconazole

10.12. Appendix 12: CYP3A Sensitive Substrates

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

Abemaciclib	Lomitapide
Acalabrutinib	Lopinavir
Alectinib	Lovastatin
Alfentanil	Lumefantrine
Aprepitant (also fosaprepitant)	Lurasidone
Atazanavir	Maraviroc
Atorvastatin	Midazolam
Avanafil	Midostaurin
Avapritinib	Naloxegol
Bosutinib	Neratinib
Brotizolam	Nisoldipine
Budesonide	Paritaprevir
Buspirone	Quetiapine
Cobimetinib	Quinidine
Conivaptan	Saquinavir
Darifenacin	Sildenafil
Darunavir	Simeprevir
Dasatinib	Simvastatin
Dronedarone	Sirolimus
Ebastine (OUS only)	Tacrolimus
Eliglustat	Ticagrelor
Elvitegravir	Tipranavir
Entrectinib	Tolvaptan
Eplerenone	Triazolam
Everolimus	Ulipristal
Felodipine	Ubrogepant
Ibrutinib	Vardenafil
Indinavir	Venetoclax
Isavuconazole (prodrug is isavuconazonium sulfate)	Vinblastine
Ivabradine	Zanubrutinib
Ivacaftor (also ivacaftor with lumacaftor, ivacaftor with tezacaftor)	

Source: University of Washington Drug Interaction Solutions List of CYP3A Sensitive Substrates accessed 14 May 2020.

10.13. Appendix 13: Other CYP-Sensitive Substrates

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

	Sensitive substrates
CYP2C8	Repaglinide
CYP2C9	Celecoxib
CYP2C19	S-mephenytoin, omeprazole
CYP2D6	Atomoxetine, desipramine, dextromethorphan, eliglustat(e), nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine

Note: sensitive substrates are drugs that demonstrate an increase in area under the concentration time curve of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug–drug interaction studies.

10.14. Appendix 14: Inhibitors and inducers of *UGT1A1*

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

Dasabuvir	Paritaprevir
Faldaprevir	Ritonavir
Ombitasvir	Telaprevir

Source: University of Washington Drug Interactions Database accessed August 2020.

10.15. Appendix 15: 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 sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local ERBs, 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 conditions 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 GCP, enabling participants to continue safely in the study, and maintaining the integrity of the study.

Informed Consent

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

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

Changes in Study Conduct During Exceptional circumstances

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

The following changes in study conduct 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.

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

Data captures

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 AEs, 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.

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 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 verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, 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.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. 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 investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.16. Appendix 16: Abbreviations

Term	Definition
Abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence.
AE	adverse event
AI	aromatase inhibitor
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
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.
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product.
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial.
BCRP	Breast Cancer Resistance Protein
BIRC	Blinded Independent Review Committee
CAP	College of American Pathologists
CBR	clinical benefit rate
CDK	cyclin-dependent kinase

CFR	Code of Federal Regulations
CFS	chemotherapy-free survival
CI	confidence interval
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CR	complete response
CRF	case report form
CRP	Clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DLT	dose-limiting toxicities
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCFR	electronic case report form
ECOG	Eastern Cooperative Oncology Group
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.

ER	estrogen receptor
ER+	estrogen receptor-positive
ERα	estrogen receptor α
EDC	electronic data capture system
EEC	endometrial endometrioid cancer
ERB	Ethical Review Board
ET	endocrine therapy
FES	F-fluoroestradiol
FSH	follicular stimulating hormone
G	grade
GCP	Good Clinical Practice
GDPR	EU General Data Protection Regulation
HER2-	human epidermal growth factor receptor 2 negative
HR	hormone receptor
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

INR	international normalized ratio
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 Board
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 allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web response system
mBC	metastatic breast cancer

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 or 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.
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NIMP	Non-investigational Medicinal Product See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
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
P-gp	P-glycoprotein 1

PET	positron emission tomography
PI3K	phosphoinositide 3-kinase
PK/PD	pharmacokinetics/pharmacodynamics
P-gp	p-glycoprotein
PGR	progesterone receptor
PFS	progression-free survival
PO	orally
PR	partial response
PRO/ePRO	Patient-reported outcomes/electronic patient-reported outcomes
PS	performance status
PT	prothrombin time
QD	once daily
SAC	statistical analysis center
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	stable disease
SERD	selective estrogen receptor degrader
SoA	Schedule of Activities
SOC	standard of care
STFU	short-term follow-up
SMD	Senior Management Designee
SRE	skeletal-related event

SUSARs	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.
TTC	time to chemotherapy
UGT1A1	UDP Glucuronosyltransferase Family 1 Member A1
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.17. Appendix 17: 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]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to increase the sample size for PFS between Arm A and Arm B (for the first two primary endpoints). Changes are outlined in this table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis	Updated to match changes in the main protocol	Update
Section 1.2. Schema	Removed the footnote addressing Arm B enrollment.	Arm B is now wider, so the schema shows all study arms will close at the same time.
Section 1.3. Schedule of Activities	Clarified short-term and long-term follow-up visit day; clarified footnote “a” and included details of Cycle 2 Day 15 under Foot note “c”	Correction
	Added text to second instructional comment for Bone scintigraphy line item: “...start of a new anticancer therapy...”	For consistency with radiologic imaging
Section 2. Introduction	Added Introduction/Rationale for Amendment (c)	Addition
Section 3. Objectives and Endpoints	Added row under exploratory analysis: “To assess clinical efficacy parameters of Arm C compared to Arm B” for endpoints PFS and OS	Updates to study design
Section 4.1. Overall Design; Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Clarified language regarding randomization into Arm A, B, and C; updated language regarding analysis of PFS	Updates to study design
Section 5.1. Inclusion Criteria	Criterion 3: Additional notes added to better understand criterion #3 in a global study without any changes in actual eligibility criterion. Criterion 5: removed “and FSH” from note	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 6.6.1. Imlunestrant Dose Adjustments for Treatment-Emergent, Related, and Clinically Significant Adverse Events	Included AST/ALT >8 x ULN under toxicity profile and severity for hepatotoxicity	Clarification
Section 6.1. Study Intervention(s) Administered	Edited fulvestrant paragraph, removing specific language for "1 to 2 minutes per injection," and referenced approved label Added text to exemestane paragraph; referred to approved label	Clarification
Section 7.1. Participant Discontinuation/Withdrawal from Study Treatment	Deleted sentence following bullet points stating that "discontinuation is expected to be uncommon"	Not appropriate for this study
Section 9.2. Sample Size Determination; Section 9.4.3.1 Primary Analyses; Section 9.5.2. Efficacy Interim Analyses	Increased the number of events/total sample size for the PFS between Arm A and Arm B Removed detailed enrollment assumptions in Section 9.2 and referenced the SAP	Updates to study design (sample size), and clarification
Section 9.4.3.1. Primary Analyses	Included the word "PFS"	Clarification
Section 9.4.3.3. Other Secondary Analyses	Removed language regarding measurable disease in the analysis of DoR	Clarification
Section 9.4.7.1. Exploratory Analyses	Added "…unless otherwise stated"; added language regarding Arm C and Arm B comparison	Clarification and updates to study design
Section 9.5.2. Efficacy Interim Analyses	Updated the table "Stopping Boundaries for Each Analysis between Arm A and Arm B in the ITT Population"	Updates to study design (stopping boundaries)
Throughout	Minor editorial and formatting changes	Minor, therefore, not detailed

Amendment b: 17-Aug-2022

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the primary objective with *ESR1*-mutation detected population. Additional edits have been made to incorporate emerging data and to provide clarifications in response to site and regulatory feedback.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives and Endpoints	Added new primary objective and endpoint for progression-free survival (PFS) in the *ESR1*-mutation detected population	Updated to integrate evolving clinical data relevant to this trial

Section # and Name	Description of Change	Brief Rationale
	Added new secondary objective and endpoint for overall survival (OS) in the *ESR1*-mutation detected population Removed secondary endpoint for investigator-assessed PFS by *ESR1* mutation status in plasma/ctDNA Clarified the patient population (ITT or *ESR1*-mutation detected) for both objectives and endpoints	
1.3 Schedule of Activities	Revised the instructions for the following procedures: • Radiologic imaging according to RECIST • Brain imaging • Bone scintigraphy • FSH and estradiol levels • Pregnancy test • Fasting lipid testing • Local ECG • PK sample • Biomarker plasma sample • PRO Added "see instructions" for PRO for the "Study Treatment" study period Removed "at the end of this period" from footnote "a" defining Short-term follow-up Revised footnote "b" to revise the intervals relative to Cycle 1 Day 1 to evaluate tumor response Revised footnote "c" regarding Cycle 1 Day 15	Revisions were made to these sections to provide clarity and make corrections. No new activities were added.
1.3.1 Schedule of Assessments for Patient-Reported Outcomes	Revised the instructions to remove administration of the following patient-reported outcomes during short-term follow-up: • EORTC QLQ-C30 • EORTC IL 19	Clarification
2 Introduction	Revised section to provide rationale for addition of PFS in the *ESR1*-mutation detected population	Updated to reflect changes in objectives and endpoints
1.1 Synopsis; 4.1 Overall Design	Revised section based on changes made in Section 3 and Section 5 (inclusion criterion 5)	Updated to include emerging information
5.1 Inclusion Criteria	Criterion 3: Revised 3a-c criteria for locally advanced (not amenable to curative treatment by surgery) or metastatic disease	Additional clarity and to maintain a patient population reflective of the standard of care

Section # and Name	Description of Change	Brief Rationale
	Criterion 5: Revised to allow the Sponsor to limit the number of participants enrolled onto this study who have NOT received a prior CDK4/6 inhibitor	Edited to maintain a patient population reflective of the standard of care
	Criterion 7a: Addition of a note to include participants established on a less frequent GnRH agonist administration schedule	Operational/editorial
	Criterion 10: Revised measured creatinine clearance and hemoglobin laboratory values	Regulatory suggestion
5.2 Exclusion Criteria	Criterion 20: "Consent" replaced by "randomization"	Operational/editorial
	Criterion 21: Changed the number of days prior to randomization for participants undergoing major surgery from 14 to 28 days	Regulatory suggestion
	Criterion 23i: Added "at several consecutive days of assessment"	Operational/editorial
	Criterion 24: "Active symptoms" replaced by "pre-existing medical condition"	Operational/editorial
5.4 Screen Failures	Removed "If the results of a repeated laboratory test meet the eligibility criteria, that laboratory test must be repeated to confirm eligibility"	Clarification
6.1 Study Intervention(s) Administered	Updated instructions for imlunestrant administration	Clarification
6.6 Dose Modification	Replaced the sub-heading "The sections below detail dose modification and delays of imlunestrant" with "General Considerations for Dose Delays"	Clarification
8.1.1 Efficacy Assessments at Baseline and during Study Treatment	Revised the brain imaging instructions to align with changes in schedule of activities	Clarification
8.2.2.1 Hepatic Safety Monitoring	Added "For patients that meet the criteria above, whenever possible and as clinically appropriate, continue monitoring after discontinuation of imlunestrant until values are back to baseline".	Operational
8.8 Biomarkers	Added patient's consent to be obtained to undergo a fresh tumor biopsy prior to treatment if patients do not have adequate archival tumor tissue available Revised the eligibility criteria if archival tissue is not available and a fresh tumor biopsy cannot be performed Added "Personal identification information that can directly identify a	Operational/editorial

Section # and Name	Description of Change	Brief Rationale
	patient will not be included with the sample".	
9.1 Statistical Hypotheses	Added hypotheses 2 for *ESR1*-mutation detected population	Updated to reflect changes in objectives and endpoints and to incorporate emerging information
1.1 Synopsis; 4.1 Overall Design; 9.2 Sample Size Determination	Added the hypothesis for *ESR1*-mutation detected population Added the graphical approach that will be used to test the PFS hypotheses and the OS hypotheses	Updated to reflect changes in objectives and endpoints and to incorporate emerging information
4.1 Overall Design; 9.4.3.1 Primary Analyses	Added the analysis for *ESR1*-mutation detected population Clarified the patient population (ITT or *ESR1*-mutation detected)	Updated to incorporate emerging information
9.4.3.2 Key Secondary Analyses	Added reference to SAP for the graphical approach for OS endpoints that will be tested hierarchically Added OS between Arm A and Arm B in the *ESR1*-mutation detected population Clarified the patient population (ITT or *ESR1*-mutation detected) Added reference to SAP for analysis of each OS endpoint that will be conducted in the same analysis populations for PFS	Updated to incorporate emerging information
9.4.3.3 Other Secondary Analyses	Clarified the patient population (ITT or *ESR1*-mutation detected) Removed PFS (investigator-assessed) by *ESR1* mutation status (in plasma/ctDNA)	Clarification
9.4.4 Patient-Reported Outcomes and Medical Resource Utilization	Clarified the patient population (ITT or *ESR1*-mutation detected) for each comparison	Clarification
9.4.7.1 Exploratory Analyses	Clarified the patient population (ITT or *ESR1*-mutation detected) for each comparison	Clarification
9.4.7.3 Biomarker Analyses	Updated with baseline *ESR1* mutation status (mutation detected versus mutation not detected)	Clarification

Section # and Name	Description of Change	Brief Rationale
9.5.2 Efficacy Interim Analyses	Revised the investigator-assessed events for the two interim analyses planned for the primary endpoint of PFS between Arm A and Arm B in the ITT population Updated the hazard ratio to be recommended by the DMC to stop the trial for futility Updated the number of events in the ITT population Updated stratified log-rank test p-value Updated second interim analysis plan for the PFS between Arm A and Arm B in the ITT population Added interim analysis plan for PFS between Arm A and Arm B in the *ESR1*-mutation detected population Revised stopping boundaries for each analysis between Arm A and Arm B in the ITT population based on the initial allocation of alpha	Updated to reflect changes in objectives and endpoints and to incorporate emerging information
10.3 Appendix 3: Protocol JZLC RECIST Criteria 1.1	Revised the specifications by methods of measurement to include the timeline exception of obtaining baseline bone scintigraphy	Operational clarification
10.4 Appendix 4: Clinical Laboratory Tests	Formatted table for clinical laboratory tests. Revised footnote c to include FSH and estradiol at screening for women <60 years of age	Operational/editorial for additional clarity
10.7 Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information	Minor revisions made for women in the following categories to not be considered as woman of childbearing potential • Premenopausal female • Postmenopausal female	Operational/editorial for additional clarity
10.9 Appendix 9: Liver Safety: Suggested Actions and Follow-Up Assessments	Formatted table for hepatic evaluation tests	Editorial for additional clarity
10.10 Appendix 10: Country-specific Requirements	Added appendix to include EU specific requirements for the following countries: • Belgium • Czech Republic • France • Germany • Italy, and • Spain	Regulatory request

Section # and Name	Description of Change	Brief Rationale
10.10.1 Discontinuation of Inadvertently Enrolled Patients in Germany	Removed duplicate section to align with Germany appendix (Section 10.10.4)	Editorial
10.16 Appendix 16: Abbreviations	Updated abbreviations	Editorial
11 References	Updated citations	Editorial
Throughout	Minor editorial and formatting changes	Minor, therefore, not detailed

Amendment a: 8-Oct-2021

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

Overall Rationale for the Amendment:

The primary purpose of this amendment is to incorporate a new treatment arm into the study design. Additional edits have been made to incorporate emerging data and to provide clarifications in response to site and regulatory feedback.

Section # and Name	Description of Change	Brief Rationale
Protocol Approval Page	Removed page	Medical monitor name and contact information will be provided in separate document
Title Page; 1.1 Synopsis; 1.2 Schema; 1.3 Schedule of Activities; 1.3.2 Sampling Schedules for Pharmacokinetics; 4.1 Overall Design; 6.1 Study Intervention(s) Administered; 6.1.4 Arm C Imlunestrant + Abemaciclib: General Dosing Instructions; 6.6.4 Re-escalation Criteria; 8.4 Treatment of Overdose; 8.5 Pharmacokinetics; 9 Statistical Considerations	Added treatment arm 3, imlunestrant plus abemaciclib, to study design; language added throughout protocol to reflect addition of abemaciclib to study design and analyses	New arm added to study design to incorporate abemaciclib + imlunestrant combination
1.1 Synopsis; 3 Objectives and Endpoints	Added new primary, secondary, and exploratory objectives	New objectives added for Arm C
1.3 Schedule of Activities	Added additional visits / assessments for Arms A and C	Added for abemaciclib safety monitoring
1.3 Schedule of Activities	Added clarification that patient diary is for patients randomized to Arms A or C	Clarification

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Clarified long-term follow-up adverse event collection	Clarification
1.3 Schedule of Activities	Added collection windows for hematology and clinical chemistry	Added for flexibility
1.3 Schedule of Activities; 5.1 Inclusion criteria	Added on study and follow-up FSH and estradiol procedures; updated ovarian function requirements in Inclusion #5	Allowance of more flexible GnRH agonist administration
1.3 Schedule of Activities	Removed Visit 0 PRO assessment	PROs will not be collected at Visit 0
1.3.1 Schedule of Assessments for Patient-Reported Outcomes	Revised Instructions	Operational/editorial
2 Introduction; 2.1 Study rationale; 2.2 Background	Revised section to provide introduction to CDK4/6 inhibitors, rationale and background for abemaciclib combination, and remove information detailed in other documents	Updated to reflect changes in study design and to remove information detailed in other documents
2.3 Benefit/Risk Assessment	Updated benefit/risk assessment to include more recent information and to include abemaciclib	Updated to reflect changes in study design and to incorporate emerging information
4.3 Justification for Dose	Added justification for imlunestrant + abemaciclib combination dosing	Added to provide rationale/justification for combination dosing
5.1 Inclusion Criteria	Criterion 3: Specified that prior treatment with CDK4/6 inhibitor is expected if treatment was approved and can be reimbursed	Regulatory suggestion
5.1 Inclusion Criteria	Criteria 6 and 7: Added additional contraceptive requirements for patients receiving fulvestrant	Inadvertent omission
5.1 Inclusion Criteria	Criterion 10: changed total bilirubin ≤3.0 times ULN to ≤2.0 times ULN	Modified for abemaciclib
5.2 Exclusion Criteria	Criterion 15: Specified that patients that have previously completed exemestane may not receive exemestane if randomized to the control arm	Alignment with standard of care
5.2 Exclusion Criteria	Criterion 24: added examples of medical conditions precluding participation	Modified for abemaciclib
6.1 Study Intervention(s) Administered; 6.1.4 Arm C Imlunestrant + Abemaciclib: General Dosing Instructions	Added dosing information for abemaciclib	Added to reflect updated study design
6.1.2 Arm A Imlunestrant: General Dosing Instructions	Updated statement regarding effect of imlunestrant on coagulation	Updated to include emerging information

Section # and Name	Description of Change	Brief Rationale
6.2.3 Arm C Preparation / Handling / Storage: Imlunestrant + Abemaciclib	Added details for abemaciclib	Added to reflect updated study design
6.5 Concomitant Therapy	Added instructions for documentation of concomitant therapy; added details for abemaciclib	Documentation instructions added for clarification; abemaciclib details added to reflect updated study design
6.5.1 Palliative Medicine and Supportive Care; 8.1.1 Efficacy Assessments at Baseline and during Study Treatment	Added instructions for patients with bone metastases present on baseline imaging	Provide clarity of when RANK-L targeted agents may be initiated while on study
6.5.2 Supportive Management for Diarrhea	Updated supportive management instructions	Alignment with abemaciclib guidance
6.6 Dose Modification; 6.6.1 Imlunestrant Dose Adjustments for Treatment-Emergent, Related, and Clinically Significant Adverse Events; 6.6.2 Dose Modifications for Endocrine Therapy of Investigator's Choice; 6.6.3 Dose Modifications for Abemaciclib	Revised sections; added abemaciclib dose modification guidance	Revised dose modification guidance for imlunestrant for readability and consistency with abemaciclib guidance; added abemaciclib guidance to align with updated study design
6.7.1 Continued Access	Removed unblinding language	No blinding in study
8.2.4 Guidance for Monitoring Renal Function; 8.2.5 Guidance for Venous Thromboembolic Events; 8.2.6 Guidance for Interstitial Lung Disease/Pneumonitis	Added new safety sections	Added sections for abemaciclib-related safety guidance
8.3 Adverse Events, Serious Adverse Events, and Product Complaints	Clarified that abnormal laboratory values should only be reported if they are clinically relevant	Clarification
8.8 Biomarkers	Removed statement regarding additional samples for biomarker research; specified that archival blocks with be returned to the study site upon request	Operational; clarification

Section # and Name	Description of Change	Brief Rationale
8.9.1 Patient-Reported Outcomes; 8.9.3 EORTC IL19: Physical Function; 8.9.6 mBPI-sf; 8.9.7 Worst Pain NRS; 8.9.8 PRO-CTCAE Items for Diarrhea and Injection Site Pain and Swelling	Updated descriptions of questionnaires and use on study	Clarification/operational
10.1.3 Informed Consent Process	Specified investigator will explain a description of the investigational drug	Clarification
10.4 Appendix 4: Clinical Laboratory Tests	Revised guidance for abnormal laboratory values; added statement for local chemistry results for enrollment decisions; removed urinalysis; added cystatin c; revised pregnancy/hormone testing	Guidance revised for clarification; operational clarification; urinalysis removed due to not being part of study assessments, cystatin c added as part of abemaciclib renal monitoring; revised pregnancy/hormone testing to include pregnancy and postmenopausal status
10.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording,	Removed statement for post-baseline CTCAE grading	Grading will be performed per CTCAE version 5.0 for all items
Evaluating, Follow-Up, and Reporting		
Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information	Specified non-highly effective methods of contraception are not allowed	Specification for safety
10.9 Appendix 9: Liver Safety: Suggested Actions and Follow-Up Assessments	Provided additional clarifications for hepatic evaluating testing	Clarification
10.10 Appendix 10: Country-specific Requirements	Changed country-specific guidance from UK to Germany	Regulatory request
10.14 Appendix 14: Inhibitors of P-glycoprotein	Removed appendix	Appendix no longer applicable based on new data
Throughout	Changed LY3484356 to imlunestrant, where applicable	Editorial
Throughout	Minor editorial and formatting changes	Minor, therefore not detailed

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