Protocol Addendum I3Y-MC-JPCW(d)

eMonarcHER: A Randomized, Double Blind, Placebo-Controlled Phase 3 Study of Abemaciclib plus Standard Adjuvant Endocrine Therapy in Participants with High-Risk, Node-Positive, HR+, HER2+ Early Breast Cancer Who Have Completed Adjuvant HER2-Targeted Therapy

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Title Page

Protocol Title:

eMonarcHER: A Randomized, Double Blind, Placebo-Controlled Phase 3 Study of Abemaciclib plus Standard Adjuvant Endocrine Therapy in Participants with High-Risk, Node-Positive, HR+, HER2+ Early Breast Cancer Who Have Completed Adjuvant HER2-Targeted Therapy

Protocol Number: I3Y-MC-JPCW

Amendment Number: d

Compound: Abemaciclib (LY2835219)

Study Phase: 3

Short Title:

eMonarcHER: A Phase 3 Study of Abemaciclib plus Standard Adjuvant Endocrine Therapy in Participants with High-Risk, Node-Positive, HR+, HER2+ Breast Cancer

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

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

Approval Date: 14-Feb-2022 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (c)	*14-Dec-2021*
Amendment (b)	*20-May-2021*
Amendment (a)	*06-Apr-2021*
Original Protocol	*08-Dec-2020*

Amendment [d]

This amendment is considered to be substantial.

Overall Rationale for the Amendment:

Amendment (d) is necessary to allow for unblinding of participants following the decision to permanently close enrollment and proceed towards early termination. This amendment will allow for participants and investigators to make informed decisions regarding continuation or discontinuation of participation. Additionally, this update reflects the new AE monitoring as primary endpoint, removal of efficacy endpoints and other secondary/tertiary endpoints, the total number of patients enrolled, and that no new patients will be enrolled.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 2.3.1.1 Study Intervention; 2.3.2 Benefit Assessment; 2.3.3 Overall Benefit: Risk Conclusion; 4.1 Overall Design; 5 Study Population; 6.1 Study Intervention(s) Administered; 7.1 Discontinuation of Study Intervention; 7.2.1 Discontinuation of Inadvertently Enrolled Participants; 7.2 Participant Discontinuation/Withdrawal from the Study; 7.2.2 Discontinuation after Amendment (d)	Added details that no new patients will be enrolled into the study and that all currently enrolled patients will be unblinded	See Overall Rationale for Amendment
1.3 Schedule of Activities; 1.3.2 Pharmacokinetic, Genetics, and Biomarker Sampling Schedule; 8.5 Pharmacokinetics; 8.7 Genetics; 8.8 Biomarkers	Removed PK and biomarker sample collection from study schedule; specified that no additional PK analyses will be performed; specified no additional blood samples for genetics/biomarker analyses will be collected	Alignment with decision to remove PK and biomarker collection from study
1.3.1 Continued Access Schedule of Activities	Added schedule to protocol	Added for participants currently on study

1.1 Synopsis; 3 Objectives and Endpoints; 3.1 Objectives and Endpoints for Amendment (d)	Added objectives for amendment (d)	See Overall Rationale for Amendment
4.4 End of Study Definition; 6.7.1 Study Completion Definition	Updated end of study and study completion definitions	Alignment with study update
6.3 Measure to Minimize Bias: Randomization and Blinding; 6.3.1 Unblinding at Interim Analyses; 6.3.2 Emergency Unblinding; 6.3.3 Inadvertent Unblinding; 6.3.4 Amendment (d) Patient Unblinding	Aligned sections with decision to unblind all participants	See Overall Rationale for Amendment
6.4 Study Intervention Compliance	Specified that study will not evaluate compliance/PK assessments; specified participants will not complete a Patient Dosing Diary	Alignment with study updates
6.5 Concomitant Therapy	Specified that use of concomitant medications will not be collected as of amendment (d)	Alignment with study updates
6.6 Dose Modification; 6.6.1 Dose Suspension and Cycle Delay	Specified that dose modifications, suspensions, and delays of abemaciclib will be at the investigator's discretion	Alignment with study updates
7.3 Lost to Follow up	Removed collection of survival status	No longer applicable to study
8.1.1 Imaging and Recurrence Assessment; 8.1.2 Appropriateness of Assessments	Specified that imaging decisions should continue per investigator's discretion; specified no additional efficacy data will be collected	Alignment with study updates
8.2 Safety Assessments; 8.2.1 Clinical Safety Laboratory Assessments; 10.2 Appendix 2: Clinical Laboratory Tests	Specified that clinical laboratory test selection/timing/frequency will be at the investigator's discretion; central labs will not be collected	Alignment with study updates
8.2.2 Hepatic Safety Monitoring	Updated safety data capture instructions	Alignment with study updates
8.10 Health Economics; 8.10.1 Patient-Reported Outcomes; 8.10.2 Electronic Participant Daily e-Dairy Assessment; 8.10.3 Healthcare Resource Utilization	Specified that no additional PRO questionnaires or assessments will be collected	Alignment with study updates

9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.4.1 General Considerations; 9.4.2 Primary Endpoint(s); 9.4.3 Secondary Efficacy Endpoint(s); 9.4.4 Tertiary/Exploratory Efficacy Endpoint(s); 9.4.5 Safety Analyses; 9.4.6.3 Concomitant Therapy; 9.4.6.4 Treatment Compliance; 9.4.6.5 Extent of Exposure; 9.4.6.6. Post-Study intervention Therapy; 9.4.6.7 Subgroup Analyses; 9.4.6.8 Pharmacokinetic and Exposure-Response Analyses; 9.4.6.9 Biomarker Analyses; 9.4.6.10 Health Economics Analyses; 9.5.1 Interim Analyses for Efficacy/Futility; 9.5.2 Interim Analyses for Safety	Revised sections to state which analyses will not be performed	Alignment with study updates
10.1.6 Data Quality Assurance	Specified that eCOA data will not be collected, analyzed, or reported as of amendment (d)	Alignment with study updates
10.1.9 Publication Policy	Specified that the study results will not be published	Alignment with study updates
10.8 Appendix 8: Protocol JPCW Breast Cancer Recurrence and Other Cancer Events	Removed appendix	No longer applicable for study
Throughout the protocol	Minor editorial and formatting changes	Minor; therefore not detailed

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1. Protocol Summary

1.1. Synopsis

Protocol Title: eMonarcHER: A Randomized, Double Blind, Placebo-Controlled Phase 3 Study of Abemaciclib plus Standard Adjuvant Endocrine Therapy in Participants with High-Risk, Node-Positive, HR+, HER2+ Early Breast Cancer Who Have Completed Adjuvant HER2-Targeted Therapy.

Short Title: eMonarcHER: A Phase 3 Study of Abemaciclib plus Standard Adjuvant Endocrine Therapy in Participants with High-Risk, Node-Positive, HR+, HER2+ Breast Cancer.

Rationale:

Study I3Y-MC-JPCW (JPCW; eMonarcHER) is a Phase 3 study that will evaluate the potential for abemaciclib, a potent inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6), to enhance adjuvant endocrine therapy (ET) compared to standard adjuvant ET alone, in participants with node-positive, hormone receptor positive (HR+), human epidermal growth factor receptor-2 positive (HER2+) early breast cancer who are at high risk of disease recurrence.

The currently approved standards of care offered to this patient population include a combination of systemic treatments with (neo)adjuvant cytotoxic chemotherapy, HER2-targeted therapy, ET, surgery, and radiotherapy, if clinically indicated. Despite advances in therapeutic options for early-stage breast cancer, a high-risk subpopulation receives suboptimum benefit and may demonstrate resistance to anti-estrogen therapy at the time of recurrence. This phenomenon could be explained as a consequence of cancer cell clones that survive through or evolve during standard endocrine and HER2-targeted therapies.

In HR+, HER2+ early breast cancer, the average time-to-disease recurrence is less than 3 years from the initiation of adjuvant HER2-targeted therapy (Chumsri et al. 2019). Once distant disease recurrence occurs, the disease is considered metastatic and incurable. There remains a large unmet need for patients with HR+, HER2+ breast cancer who are at high risk of recurrence, including those with node-positive disease. Therefore, improving on the absolute benefit observed with standard of care adjuvant ET is necessary for this high-risk subgroup.

Nonclinical and clinical data support the activity of abemaciclib in HER2+ breast cancer. Study I3Y-MC-JPBZ (MonarcHER) provided a proof of concept for the activity of abemaciclib in combination with HER2-targeted therapy, trastuzumab, and ET in HR+, HER2+ advanced disease (Tolaney et al. 2020a). In addition, abemaciclib combined with ET has demonstrated clinical efficacy in HR+, HER2-negative advanced breast cancer, including those who are endocrine resistant (Sledge et al. 2017; Sledge et al. 2019). In the adjuvant setting, a recent study demonstrated that the addition of abemaciclib to ET improved invasive disease-free survival (IDFS) compared to standard of care endocrine monotherapy in patients with node-positive, HR+, HER2-negative early breast cancer at high risk of disease recurrence (monarchE) (Johnston et al. 2020).

We are proposing this Phase 3 adjuvant study in patients with high-risk, node-positive, HR+, HER2+ early breast cancer. This proposed study builds on the benefit observed in monarchE in the HR+ early breast cancer patients, aiming to improve the absolute benefit of adjuvant ET by

investigating the activity of abemaciclib in combination with ET as adjuvant treatment for HR+, HER2+ patients who have completed standard HER2-targeted therapy in the adjuvant setting.

The development of novel therapeutic strategies is an important unmet medical need for patients with this disease, as current standard of care is suboptimal for these patients. Several factors have been identified in the literature that are associated with high risk of disease recurrence in this group, such as presence of tumor involvement in the axillary lymph node at the time of diagnosis, larger primary breast tumors (≥5 cm), higher histologic grade, and residual disease after neoadjuvant treatment (Lambertini et al. 2019; von Minckwitz et al. 2017; von Minckwitz et al. 2019).

For eMonarcHER, high risk has been defined by the following characteristics at the time of definitive surgery:

- Participants who received neoadjuvant chemotherapy along with HER2-targeted treatment and
  - residual disease in at least 1 axillary lymph node or
  - a residual tumor measuring ≥5 cm, or
  - a residual tumor of any size that has direct extension to the chest wall and/or skin (ulceration or skin nodules).
- Participants who had definitive surgery prior to systemic therapy, completed adjuvant chemotherapy along with HER2-targeted therapies (trastuzumab and pertuzumab), and
  - tumor involvement in ≥4 ipsilateral axillary lymph nodes, or
  - tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) and
    - histological Grade 3, or
    - primary tumor size of ≥5 cm.

Objectives and Endpoints (prior to amendment [d])

Objectives	Endpoints
Primary	
• To compare the efficacy of abemaciclib plus physician's choice ET versus placebo plus physician's choice ET in the study population.	• IDFS as defined by the STEEP System (Hudis et al. 2007)
Secondary	
• To compare the efficacy of abemaciclib plus ET versus placebo plus physician's choice ET in the study population.	• OS • DRFS • Incidence of CNS metastases as the first site of disease recurrence
• To assess the safety profile of abemaciclib plus physician's choice ET versus placebo plus ET in the study population.	• Safety, including but not limited to TEAEs SAEs, hospitalizations, clinical laboratory tests, vital signs, and physical examinations

Objectives	Endpoints
• To evaluate participant-reported symptoms, function and global health status/QOL (EORTC QLQ-C30).	• To compare EORTC QLQ-C30 scales between treatment arms
• To evaluate health status in the study population to inform decision modeling for health economic evaluation using the EQ-5D 5L.	• The EQ-5D 5L the index score and the single-item health status measure
• To evaluate the PK of abemaciclib.	• Abemaciclib concentrations

Abbreviations: CNS = central nervous system; DRFS = distant relapse-free survival; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30; ET = endocrine therapy; IDFS = invasive disease-free survival; OS = overall survival; PK = pharmacokinetics; QOL = quality of life; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Objectives and Endpoints as of Amendment (d)

Objectives	Endpoints
To monitor the safety of abemaciclib plus physician's choice ET in the study population.	AEs and SAEs per CTCAE v5.0

Abbreviations: AEs = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; SAEs = serious adverse events

Overall Design

eMonarcHER is a Phase 3 multicenter, randomized, double-blinded, placebo-controlled trial in participants with high-risk, node-positive, HR+, HER2+ early breast cancer who have completed adjuvant HER2-targeted therapy.

Approximately 2450 participants will be enrolled in a 1:1 randomization. Participants will be assigned to blinded study drug (abemaciclib or placebo) plus ET. Study intervention will be given for up to 26 cycles (approximately 2 years, where a cycle = 28 days), or until evidence of disease recurrence or another discontinuation criterion is met, whichever occurs first.

Endocrine therapy will be taken as prescribed during the on-study intervention period (approximately 2 years). After the on-study intervention period, standard adjuvant ET should continue for a duration of 3 to 8 additional years, for a total duration of up to 10 years, if deemed medically appropriate.

Standard approved adjuvant ET is per physician's choice (such as, tamoxifen or an aromatase inhibitor, with or without ovarian function suppression per standard practice). Adjuvant treatment with fulvestrant is not allowed at any time during the study.

As of amendment (d), no new patients will be enrolled, investigators and patients will be unblinded to treatment arm.

Disclosure Statement: This is a parallel treatment study with 2 arms that are blinded.

Changes Upon Approval of Amendment (d)

The study was determined to be no longer feasible due to slow accrual and changes in the treatment landscape for HER2+ breast cancer that are anticipated to improve patient outcomes and diminish the unmet medical need; therefore, enrollment was terminated.

After approval of amendment (d), and according to local regulations, participants who are on study treatment will be unblinded and enter the Continued Access period and follow the Continued Access SoA (Section 1.3). If the investigator determines that continuation of abemaciclib may offer potential benefit to participants receiving study treatment, participants may continue to receive study treatment in the Continued Access period for a maximum of 26 cycles until any of the criteria for discontinuation are met (Section 7.1). Investigators will perform standard procedures and tests for breast cancer surveillance and management. The choice and timing of the tests will be at the investigator's discretion. The Sponsor will not routinely collect the results of these assessments unless they provide source documentation for an AE. Participants receiving placebo will be discontinued.

The sole primary endpoint will be AE monitoring for participants who remain on abemaciclib.

Patients who discontinue therapy will have a short-term follow-up visit. Long-term follow-up does not apply.

Number of Participants:

Approximately 2450 participants were planned to be randomized in the study; however, as of amendment (d), enrollment and randomization of new patients was stopped and unblinding of participants was allowed. Approximately 115 participants were randomized into the study.

Intervention Groups and Duration:

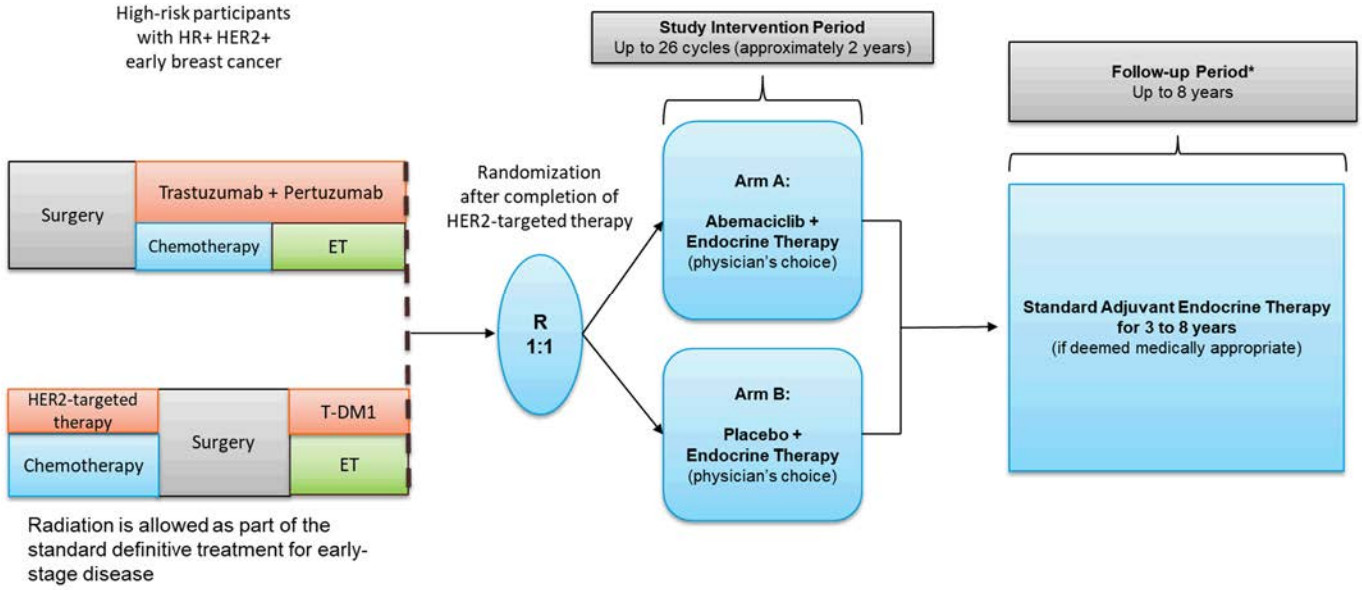
Arm	Arm A (experimental)		Arm B (control)	
Intervention	Abemaciclib	ET	Placebo	ET
Dose	150 mg (3, 50-mg tablets	Standard adjuvant ET of physician's choice	3 placebo tablets	Standard adjuvant ET of physician's choice
Schedule	BID		BID	
Route	PO		PO	

Abbreviations: BID = twice a day, at least approximately 6 hours apart; ET = endocrine therapy; PO = by mouth.

Data Monitoring Committee:

As of amendment (d), there will be no data monitoring committee.

1.2. Schema



* Upon approval of amendment (d), the study will no longer include long-term follow-up evaluation.

Abbreviations: ET = endocrine therapy; HR+ = hormone receptor-positive; HER2+ = human epidermal growth factor receptor-2 positive; R = randomization; T-DM1 = trastuzumab emtansine.

Note: Patients in both arms will receive 26 cycles of study intervention during the treatment period unless meeting a criterion for discontinuation.

1.3. Schedule of Activities (SoA)

Upon approval of amendment (d), participants will follow the Continued Access SoA in Section 1.3.1.

Day 1 is the first dose of blinded study drug following randomization (abemaciclib or placebo), regardless of if the participant is receiving ET immediately prior to randomization. The first dose of blinded study drug and physician's choice of ET should be initiated no later than 7 days following randomization.

Clinic visits:

Clinic visits will occur more frequently early in the study intervention period. For the first 2 cycles, participants will return to the clinic every 2 weeks (14 ± 3 days); that is on Days 1 and 15 of Cycles 1 and 2. For Cycles 3 and 4, clinic visits will occur on Day 1 of each cycle (±5 days). Beginning with Cycle 6, clinic visits occur on Day 1 (±5 days) of every third cycle (Cycles 6, 9, and 12). Starting with Cycle 12, participants return to clinic on Day 1 (±5 days) of every sixth cycle (Cycles 12, 18, and 24) and again at the completion of Cycle 26.

Telephone visits:

Telephone visits will occur on Day 1 (±5 days) of Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22 and 26.

Summary of Visit Type (in-clinic or phone visit) by Cycle									
Cycle	**Visit type**	**Cycle**	**Visit type**	**Cycle**	**Visit type**	**Cycle**	**Visit type**	**Cycle**	**Visit type**
C1[a]	Clinic	C2[a]	Clinic	C3	Clinic	C4	Clinic	C5	Phone
C6	Clinic	C7	Phone	C8	Phone	C9	Clinic	C10	Phone
C11	Phone	C12	Clinic	C13	None	C14	Phone	C15	None
C16	Phone	C17	None	C18	Clinic	C19	None	C20	Phone
C21	None	C22	Phone	C23	None	C24	Clinic	C25	None
C26[b]	Phone/clinic	V801	Clinic	V802	Clinic	V803-XX		Clinic preferred	

Abbreviations: C = cycle; V = visit.

[a] C1 and C2 visits are every 2 weeks.

[b] C26 Day 1 is a phone visit; end of C26 is a clinic visit.

Detection of symptoms suspicious of disease recurrence is highly important. The investigator or another medically qualified individual is expected to conduct a comprehensive and systematic assessment of these symptoms during clinic and phone visits. Of note, the protocol does not prohibit more frequent monitoring by imaging, if judged necessary by the investigator for an individual patient.

Short-term follow-up:

Participants discontinuing study intervention (either early discontinuation or at completion of 26 cycles after initiation of abemaciclib) will return for an in-clinic visit (Visit 801). This visit will include physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, concomitant medication, adverse event collection, disease symptoms assessment, central chemistry, and hematology, and return of study drug.

The short-term follow-up visit takes place 30 days (±5 days) after 1 of the following time points, whichever occurs first:

- after the completion of 26 cycles of the on-study intervention period.
- after discontinuation criteria are met (Section 7.1) and decision is made for the participant to discontinue placebo as required at the time of unblinding or abemaciclib prior to the completion of the 26 cycles of the on-study intervention period.

Long-term follow-up:

Upon approval of amendment (d) the study will no longer include long-term follow-up evaluation or data collection.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Informed consent	See instructions											• ICF may be signed up to 3 months prior to C1D1. • ICF must be signed before any protocol-specific procedures are performed
Inclusion/exclusion criteria	X											See Sections 5.1 and 5.2.
Medical history	X											Including assessment of preexisting conditions and historical illnesses, and habits (such as, tobacco and alcohol use).
Cancer treatment history	X											Record prior anticancer therapy.
Concomitant medication	X		X							X		• At screening, record prior and concurrent medications. • Record all supportive care and concomitant medication continuously including over-the-counter (including herbal and dietary supplements) at every visit through V801.
Clinically directed physical examination	X		X	X	X	X	X	X	X	X	X	At each in-clinic visit.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Vital signs	X		X	X	X	X	X	X	X	X		• In-clinic visits only. Measure height (screening only), weight (D1 of each cycle and V801), and for each visit: temperature, blood pressure, pulse rate, pulse oximeter (SpO2), and respiration rate. • If vital signs were collected within 3 days of D1, they do not need to be repeated at D1.
AE collection	X		X							X	See instructions	• Any AE, including SAEs are collected continuously at every in-clinic and phone visit and throughout the on-study intervention period and short-term follow-up. Only SAEs will be reported up to 5 years during long-term follow-up period, regardless of causality to study intervention treatment. • CTCAE Version 5.0
ECOG PS	X		X		X		X	X	X	X		• C1, C2, and all subsequent in-clinic visits during the on-study intervention period, and V801. • If performed ≤3 days prior to C1D1, may be used for C1D1 assessment.
ECG	X											• Single, local during screening and when clinically indicated. • Participant must be supine or near supine for approximately 5 to 10 minutes prior to collection and remain supine, but awake, during collection.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Hematology		X	X	X	X	X	X	X	X	X		• See Appendix 2, Section 10.2. • Hematology labs required for visits held at the clinic. • Hematology labs not required for phone visits; however, additional labs may be drawn as clinically indicated outside of in-clinic scheduled visits. • Sample must be taken either within 14 days of C1D1 or on C1D1.
Clinical chemistry		X	X	X	X	X	X	X	X	X		• See Appendix 2, Section 10.2. • Chemistry labs required for visits held at the clinic. • Chemistry labs not required for phone visits; however, additional labs may be drawn as clinically indicated outside of in-clinic scheduled visits. • If collected at baseline (≤14d from C1D1), then may be used in place of C1D1 collection.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Pregnancy test		X	X	See instructions								• Applies only to women of childbearing potential. • Serum pregnancy test at screening, performed locally. • Urine or serum pregnancy test ≤24 hours of C1D1, performed locally. • See Appendix 2, Section 10.2. • Note: During the on-study intervention period, local regulations and/or institutional guidelines may require additional testing.
Abdominal ± pelvic imaging (such as CT, PET/CT, MRI, ultrasound)	See instructions		See instructions							See instructions		• During screening: Abdominal ± pelvic imaging MUST be performed prior to randomization. Abdominal ± pelvic imaging performed previously as part of routine care, any time in the process of or after diagnosing the patient with the current breast cancer diagnosis may be used as the baseline assessment. • During treatment and follow-up: Abdominal ± pelvic imaging is to be performed ONLY if clinically indicated per the investigator's judgment.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Bilateral imaging (such as, diagnostic mammogram or MRI of remaining breast tissue)	See instructions		See instructions							See instructions		• During screening: Bilateral breast imaging of conserved and/or contralateral breast performed locally within 1 year prior to randomization MUST be obtained. Breast imaging performed as part of routine care within 1 year prior to randomization may be used as the baseline assessment. This is not required for patients who had bilateral mastectomy. • During treatment and follow-up: Repeat breast imaging either at yearly intervals or according to local standards as part of routine medical care. Patients who have had a mastectomy should be followed per local practice. Of note, international standard guidelines recommend breast imaging at yearly intervals. • Ultrasound alone is not sufficient for bilateral imaging.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Chest imaging (such as, PET/CT, CT, or x-ray [should include lateral and PA views])	See instructions		See instructions							See instructions		• During screening: Chest imaging MUST be performed prior to randomization. Imaging performed previously as part of routine care, any time in the process of or after diagnosing the participant with the current breast cancer diagnosis, may be used as the baseline assessment. CT scan is permitted as an alternative if this is part of routine practice. • During treatment and follow-up: Chest imaging (chest x-ray with lateral and PA views or chest CT scan) is to be performed locally and ONLY if clinically indicated per the investigator's judgment. If PET/CT is performed, additional imaging modalities are not required.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Bone nuclear imaging (such as, bone scan, PET scan, or PET/CT)	See instructions		See instructions							See instructions		• Prior to randomization: Full body bone imaging per standard clinical practice MUST be performed prior to randomization to discard or confirm potential distant disease. Bone imaging performed previously as part of routine care, any time in the process of or after diagnosing the participant with the current breast cancer diagnosis, may be used as the baseline assessment. • Post randomization and follow-up: Performed locally and ONLY if clinically indicated per investigator's judgment (for example, if participant is symptomatic for bone pain and/or if alkaline phosphatase is significantly elevated ≥3×ULN). If PET/CT is performed, additional imaging modalities are not required.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Disease recurrence assessment	X		X		X		X	X	X	X	X	• At every indicated visit (in-clinic and phone) and as clinically indicated until distant disease recurrence or death, whatever occurs first. See Section 8.1 and Section 10.8. (Appendix 8). • Assessment for changes in signs and symptoms suggestive of disease recurrence. • Assessments will also be performed for participants who discontinue treatment without an IDFS event per STEEP system (Section 10.8.) or who are randomized and never received study intervention.
Participant PRO questionnaires on site-based electronic device: EORTC QLQ-C30, FACT-GP5, PRO-CTCAE selected items, and EQ-5D 5L			X	X	X	X	See instructions	See instructions		X	See instructions	At in-clinic visits. Complete at the following timepoints prior to extensive contact with site personnel: • C1D1 (or ≤3 days prior to C1D1): Prior to starting blinded study drug • C1D15 • Cycle 2 (D1, D15) • Cycles 3-26 on D1 of in-clinic visits (at Cycles 3, 4, 6, 9, 12, 18, 24); not collected at C26 Day 28. • Short-term follow-up • Long-term follow-up until end of Year 4

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Participant PRO daily e-diary (participant subgroup)		See instructions	X	X	X	X	See instructions					• Screening: collect at least 1 day and up to 7 days of daily data in the week prior to starting blinded study drug on C1D1 • For Cycles 1, 2, and 3 only • Subgroup of approximately 300 participants will record daily e-diary information on the number of stools, diarrhea, use of loperamide, blinded study drug dosing, ET dosing, fatigue, arthralgia, and hot flashes.
Participant Paper Diary (blinded study drug)			See Instructions									• Sites distribute the paper diary to participants on C1D1. • Participants record date and times of every dose of blinded study drug taken from C1D1 through C3D1. • Patients should bring paper diary to every visit for site review.
HCRU			X		X		See Instructions	See Instructions		X	X	• Collected at in-clinic visits on Day 1 of cycles when PROs are collected. See Section 8.10.3.
Survival assessment			X							X	X	

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])											
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Post-discontinuation anticancer therapies										X	X	ET after study intervention discontinuation or other breast cancer treatment are collected until study completion, participant discontinuation from study, or death.
Administer abemaciclib/placebo			X						X			• C1D1 is defined as the date the first dose of blinded study treatment is taken by the patient. • See Section 6.1.
Administer ET			FAX						X	X		• Per standard of care as prescribed by physician. • See Section 6.1.
Abemaciclib/placebo drug accountability			X		X		X	X	X			• Document tablets dispensed and returned at C1D1, C2D1, C3D1, and every in-clinic visit thereafter during the on-study intervention period. • See Section 6.3.4.
ET compliance					X		X	X	X	See instructions		• Recorded on C2D1, C3D1, and every subsequent visit (in-clinic and phone) during the on-study intervention period. • For each ET, record the number of doses missed since the previous visit. • For follow-up period, continue to document ET treatment (including switching of ET, and discontinuation and starting dates). • See Section 6.3.4.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])												
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Sample collection												
PK			See Section 1.3.2									• Collected on C1D1, C2D1, and C3D1. See Section 1.3.2 for sample collection timing and procedure details. See procedure row for Participant Paper Diary for tracking blinded study drug timing.
Whole blood for genetic/biomarker analysis			X									See Sections 1.3.2, 8.7, and 8.8. Whole-blood sample required.
Plasma for biomarkers			X					See instructions	See instructions		See instructions	• See Sections 8.8 and 1.3.2. • Plasma collected D1 at Cycles 1, 3, 6, 12, C26 Day 28, V802, and Year 5 (first visit of Year 5). • At C1D1, must be taken before first dose. • V802 sample may be taken after V802 if missed at V802. • Year 5 sample for participants on study without IDFS event.
Serum for biomarkers			X									• See Sections 8.8 and 1.3.2. • Must be taken before first dose on C1D1.

	Screening, On-Study, and Post-Treatment Schedule of Activities (prior to amendment [d])												
	Screening		**On-Study Intervention Cycle = 28 days**							**Post-Treatment**		**Instructions**
	(Day Relative to C1D1)		**Cycle 1**		**Cycle 2**		**Cycles 3-12**	**Cycles 13-26 (even-numbered cycles only)**	**Cycle 26**	**Short-term follow-up[b]**	**Long-term follow-up[c]**	
				(±3 d)	(±3 d)		(±5 d)	(±10 d)	(±5 d)	(±5 d)	(±28 d)	
	≤28	**≤14**	**D1[a]**	**D15**	**D1**	**D15**	**D1**	**D1**	**D28**	**V801**	**V802-8XX**	**Clinic visits:** Cycles 1-4, 6, 9, 12, 18, 24, 26 (Day 28), V801, V802. **Phone visits:** Cycles 5, 7, 8, 10, 11, 14, 16, 20, 22, 26 (Day 1). For V803-8XX, clinic visits are preferred, but phone visits are acceptable if unable to attend clinic visit.
Procedure												
Tumor tissue for biomarkers		X										• See Sections 8.8 and 1.3.2. • Confirm tissue availability prior to randomization. • Breast tissue preferred; lymph node tissue is acceptable. • For participants who received neoadjuvant therapy, both a pre- and a post-neoadjuvant treatment tissue sample should be sent to the central laboratory if available.
Recurrence tissue and plasma samples (biomarker)				Collect at time of local/regional and distant disease recurrence.								• See Sections 8.8 and 1.3.2 • Tissue sample mandatory for participants who undergo biopsy to confirm recurrence.

Abbreviations: AE = adverse event; Blinded Study Intervention = abemaciclib/placebo; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; d = day; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D 5L = EuroQOL 5 Dimension 5 Level; ET = endocrine therapy; FACT-GP5 = Functional Assessment of Cancer Therapy- General item; HCRU = Health Care Resource Utilization; ICF = informed consent form; IDFS = invasive disease-free survival; MRI = magnetic resonance imaging; PA = posteroanterior; PET = positron emission tomography; PK = pharmacokinetics; PRO = patient-reported outcome; SAE = serious adverse event; ULN = upper limit of normal; V = visit.

a C1D1 = date of first dose of blinded study drug.

b The short-term follow-up visit takes place 30 days (±5 days) after the on-study intervention period discontinuation date.

c The long-term follow-up period begins the day after the short-term follow-up visit, with visits occurring every 6 months (±28 days) until end of Year 5, then annually (±28 days) from Year 6 up to Year 10 or study completion, whichever occurs first.

1.3.1. Continued Access Schedule of Activities

Continued Access Schedule of Activities

Visit	Study Interventions	Short Term Follow-Up	Instructions
	Cycle 1-26	V801	
Administer study intervention	X		See Section 6.1 for administration details Follow prescribing guidelines for routine monitoring
AE collection	X	X	Per CTCAE v5.0 Collect all AE and SAE regardless of causality

1.3.2. Pharmacokinetic, Genetics, and Biomarker Sampling Schedule

Upon approval of amendment (d), PK and biomarker samples will longer be obtained, and this section is no longer applicable for participants on study.

2. Introduction

Study I3Y-MC-JPCW (JPCW; eMonarcHER) is a Phase 3 global, randomized, placebo-controlled trial in participants with high-risk, node-positive, hormone receptor positive (HR+), human epidermal growth factor receptor-2 positive (HER2+) early breast cancer who have completed standard adjuvant HER2-targeted therapy.

This proposed study will investigate whether the addition of abemaciclib, a potent inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6), to standard adjuvant endocrine therapy (ET) post completion of HER2-targeted therapy improves invasive disease-free survival (IDFS) in participants with node-positive, HR+, HER2+, breast cancer at high risk of recurrence by improving the absolute benefit from ET.

2.1. Study Rationale

Human epidermal growth factor receptor-2 is overexpressed in approximately 20% to 25% of breast carcinomas with approximately half of these being hormone receptor positive (HR+). Human epidermal growth factor receptor-2 positive breast cancer is associated with poor prognosis and high mortality rates. Although adjuvant HER2-targeted therapies have significantly improved outcomes in patients with early-stage HER2+ breast cancer, there is a subgroup of patients who will experience invasive disease recurrence either on or shortly after completion of optimal adjuvant HER2-targeted therapy, which could ultimately become incurable. Several clinicopathological factors are known to be associated with increased risk of recurrence: Presence of axillary lymph node involvement at diagnosis, large size of the primary invasive tumor (≥5 cm), higher histologic grade and pathological residual disease after neoadjuvant treatment (Lambertini et al. 2019; von Minckwitz et al. 2017; von Minckwitz et al. 2019). The reasons associated with early recurrences are not completely understood; however, this phenomenon could be explained because cancer cell clones may survive and evolve during standard endocrine and HER2-targeted therapies. In HER2+ breast cancer tumors, cyclin D1 and CDK4 are critical drivers in cell proliferation (Goel et al. 2016).

Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of CDK4 and CDK6. CDK4 and CDK6 complex with D-type cyclins to promote cell growth by facilitating the progression of cells from the G1 to the S-phase of the mammalian cell cycle (Ortega et al. 2002). This promotion of cell growth occurs primarily by counteracting the effects of the growth suppressor retinoblastoma (Rb) protein, whereby the reversal of Rb-mediated suppression is achieved by the phosphorylation of this protein by CDK4 and/or CDK6 (Ortega et al. 2002). Preclinical studies in breast cancer models with abemaciclib indicated that sensitivity to CDK4 and CDK6 inhibition was greater in HR+ lines with luminal histology, including a subset of those that are estrogen receptor-positive (ER+), HER2+ (O'Brien et al. 2018). Work from Goel et al. suggests that CDK4 and CDK6 inhibitors can delay recurrence in a transgenic HER2+ breast cancer model. In mice models induced with HER2+ tumor formation, the onset of recurrent disease was significantly prolonged in abemaciclib-treated mice compared to the control group (median time to recurrence 108 days versus 135 days; hazard ratio=0.23; p=.035). Their observations indicated that a small number of cyclin D1-expressing tumor cells survive HER2 withdrawal, and that targeting these cells with a CDK4 and CDK6 inhibitor can prolong the time to tumor recurrence. This suggests a role for CDK4 and CDK6 inhibitors as an adjuvant

therapy for breast cancer, treating microscopic residual disease with a view to preventing disease recurrence (Goel et al. 2016).

Abemaciclib has been approved for the treatment of patients with HR+, HER2-negative, advanced or metastatic breast cancer. Indications include:

- abemaciclib in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy in post-menopausal women
- abemaciclib in combination with fulvestrant in women with disease progression following endocrine therapy, or
- abemaciclib as monotherapy in adults with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

In a more recent Phase 3 study (monarchE), the efficacy of abemaciclib in combination with ET was compared to ET alone in patients with HR+, HER2-, node-positive, early breast cancer at high risk of recurrence. High risk was defined as: ≥4 positive axillary lymph nodes; 1-3 positive axillary lymph nodes with either histologic Grade 3 and/or tumor size ≥5 cm; or 1-3 positive axillary nodes with Ki-67 index ≥20% in pre-treated breast tissue as measured by a central laboratory. At a preplanned interim efficacy analysis, the combination resulted in a statistically significant and clinically meaningful improvement in IDFS (hazard ratio=0.75; confidence interval [CI]=95% [0.60 to 0.93]; p=.01) corresponding to a 25% reduction in the risk of developing invasive disease. Two-year IDFS rates were 92.2% in the abemaciclib arm vs 88.7% in the ET arm (Johnston et al. 2020).

The Phase 1 study, Study I3Y-MC-JPBA, demonstrated preliminary clinical activity for abemaciclib in patients with HER2+ mBC (Patnaik et al. 2016). In a subset of 11 patients with HR+, HER2+ mBC, an objective response rate of 36% (N=4, of which 3 were receiving concomitant ET) and a median progression-free survival (PFS) of 7.2 months. The Phase 2 study I3Y-MC-JPBO examined the impact of abemaciclib on brain metastases in patients with breast or lung cancer and melanoma. In a subset of 27 patients with advanced HR+, HER2+ breast cancer, who received abemaciclib monotherapy (with no concomitant HER2-targeted therapy), a median extracranial progression-free survival (PFS) (per Response Evaluation Criteria in Solid Tumors [RECIST]) of 7.3 months (95% CI=3.3, 13.3) was reported (Tolaney et al. 2020b). In the Phase 2 study MonarcHER, in which patients with HR+, HER2+ mBC were enrolled, abemaciclib in combination with fulvestrant and trastuzumab showed a significant improvement in median PFS of 8.3 months vs 5.7 months in the standard of care group (chemotherapy and trastuzumab) with a hazard ratio=0.67 (95% CI=0.45, 1.00) and p=.051. The combination of abemaciclib, fulvestrant, and trastuzumab was also associated with improved overall response of 36% (vs 16% standard of care) (Tolaney et al. 2020a).

Due to the high unmet need to develop new therapeutic options for patients with node-positive, HR+, HER2+, early breast cancer at high risk of recurrence, the scientific body of evidence supportive of the anticancer activity of abemaciclib in HER2+ disease, and the recent results of improved IDFS in high-risk, HR+, HER2-negative patients in the adjuvant setting, we propose to study abemaciclib in combination with ET after completion of adjuvant HER2-targeted therapies in high-risk participants. Optimizing standard adjuvant therapy by adding novel targeted therapies is warranted for patients with early breast cancer and at high risk of disease recurrence.

For eMonarcHER, high risk has been defined by the following characteristics at the time of definitive surgery:

- Participants who received neoadjuvant chemotherapy along with HER2-targeted treatment and
    - residual disease in at least 1 axillary lymph node or
    - a residual tumor measuring ≥ 5 cm, or
    - a residual tumor of any size that has direct extension to the chest wall and/or skin (ulceration or skin nodules).
- Participants who had definitive surgery prior to systemic therapy, completed adjuvant chemotherapy along with HER2-targeted therapies (trastuzumab and pertuzumab), and
    - tumor involvement in ≥ 4 ipsilateral axillary lymph nodes, or
    - tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) and
        - histological Grade 3, or
        - primary tumor size of ≥5 cm.

2.2. Background

Breast cancer is one of the most common cancers in women in the United States (US) and Europe and is the second leading cause of cancer death in women worldwide (Siegel et al. 2019). Approximately 1% of all breast cancers are diagnosed in men (Borgen et al. 1992; Senkus et al. 2015). The HR+, HER2-negative breast cancer subtype is the most prevalent of breast cancer subtypes and accounts for approximately 70% of all breast cancers (Howlader et al. 2014). Overexpression of HER2 is predictive of treatment response and prognostic for disease recurrence and death and occurs in 20% to 25% of breast cancers, with at least half of these tumors being HR+ (Konecny et al. 2003; Ulas et al. 2015). Human epidermal growth factor receptor-2 overexpression is associated with an aggressive clinical phenotype that includes high-grade tumors, increased growth rates, early systemic metastasis, and decreased rates of disease-free and overall survival (OS) (Slamon et al. 1987; Iborra and Stickeler 2016).

Approximately 90% of patients with breast cancer are diagnosed at an early stage of their disease (Howlader et al. 2016). Such patients do not possess evidence of overt distant tumor spread and, therefore, may be treated with curative intent with surgical, radiotherapy, and systemic treatments (NCCN guidelines 2020). Depending on diagnosis, including histology, grade, tumor size, and lymph node involvement, treatment options may include neoadjuvant/adjuvant therapy with chemotherapy, ET, and HER2-targeted therapy (up to 1 year) (Goldhirsch et al. 2013; NCCN 2020). Early recurrence within the first 2 years of adjuvant ET in HR+ breast cancer is known to represent primary endocrine resistance (Cardoso et al. 2018). For patients with HR+, HER2+ early breast cancer treated with chemotherapy and trastuzumab therapies, the time to recurrence (median 2.9 years) is longer compared to patients with HR-, HER2+ tumors (median 1.9 years); however, a higher rate of relapse is noted between years 5 to 10 in patients with HR+, HER2+ breast cancer with more lymph node involvement, particularly those with N3 disease (Chumsri et al. 2019). Patients with HR+ tumors are typically treated with about 5 to 10 years of ET (AIs with or without ovarian function suppression or tamoxifen as per physician's choice) following surgery and/or completion of their cytotoxic chemotherapy according to international guidelines (Senkus et al. 2015; Cardoso et al. 2019). Women with early-stage HR+ breast cancer may initially respond to endocrine treatment; however, 15% to 20% of tumors are intrinsically

resistant to treatment, and another 30% to 40% acquire resistance to treatment over years, leading to the development of metastases and death (Anurag et al. 2018; Cortés et al. 2020)

Features that may indicate a higher risk of distant disease relapse include: large primary tumor size, involvement and degree of involvement of axillary lymph nodes with tumor (regardless of HR status), high histologic grade of the primary tumor, HER2+ tumors, or lack of pathological complete response (pCR) after neoadjuvant therapy (Senkus et al. 2015; von Minckwitz et al. 2019; Cortés et al. 2020). Specifically, patients with non-pCR after neoadjuvant chemotherapy plus HER2-targeted therapy, and patients with lymph node involvement have been reported to have worse outcomes and higher recurrence rates (Chumsri et al. 2019; von Minckwitz et al. 2019). For patients with HER2+ early breast cancer with lymph node involvement, the recurrence-free survival rate is approximately 73% compared to 89% for those with no lymph node involvement (Ulas et al. 2015). Despite the outstanding improvements in survival with the introduction of HER2-targeted agents, such as trastuzumab in the adjuvant setting, many patients, particularly those with high-risk disease, develop disease recurrence (approximately 25% to 30%) and ultimately die from their cancer (De Laurentiis et al. 2005; Slamon et al. 2011; André et al. 2014; Perez et al. 2014; Slamon et al. 2016; Cameron et al. 2017).

Recently, 2 clinical studies evaluating adjuvant HER2-targeted therapies have shown benefit in improving IDFS in participants with HER2+ early breast cancer, including those with high-risk disease. In the APHINITY study, high-risk participants with 4 or more positive lymph nodes or ≥5 cm tumors had a 3-year IDFS rate of 87.5%, each with adjuvant trastuzumab and pertuzumab combination (von Minckwitz et al. 2017). In the KATHERINE study, participants with node-positive residual disease post-neoadjuvant therapy who received trastuzumab emtansine (T-DM1) in the adjuvant setting had a 3-year IDFS rate of 83%. More specifically, participants with 2 and 3 positive regional lymph nodes at definitive surgery had 3-year IDFS rates of 81.1% and 52.0% respectively. Also notable, participants with residual tumors ≥5 cm or with direct extension into the chest wall and/or the skin had 3-year IDFS rates of 79.8% and 70% respectively. These data highlight a residual high-risk population who might benefit from additional therapies remains (von Minckwitz et al. 2019).

Beyond initial adjuvant HER2-targeted therapy, neratinib has recently been approved as extended adjuvant therapy after trastuzumab-based treatment. Neratinib showed a 2-year IDFS rate of 93.9% (95% CI=92.4, 95.2) in the neratinib group compared to 91.6% (90.0, 93.0) in the placebo group (Chan et al. 2016). However, neratinib use has not been reported as extended adjuvant treatment after trastuzumab combined with pertuzumab or TDM-1 regimens.

Importantly, despite improvements in IDFS for patients with high-risk early breast cancer, there remains an unmet medical need to provide new treatment options to further improve outcomes for HR+, HER2+ early breast cancer patients who have completed adjuvant HER2-targeted therapy and have high-risk features.

2.2.1. Trastuzumab

Based on 3 pivotal studies, 1 year of the monoclonal antibody trastuzumab-based therapy has become an established global standard of care in the adjuvant setting in patients with HER2+ early breast cancer. European Society for Medical Oncology (ESMO) clinical practice guidelines currently recommend 1 year as the standard (Cardoso et al. 2019). Trastuzumab binds to the extracellular domain intravenous (IV) of HER2, thereby inhibiting downstream cell signaling

that is implicated in cell proliferation, survival, motility, and adhesion (Ross et al. 2009). In the preoperative setting, combination of trastuzumab with or without pertuzumab plus chemotherapy is recommended for patients with high-risk breast cancer. Post operatively, for patients with high risk for recurrence and/or non-pCR after neoadjuvant therapy, HER2-targeted therapy with trastuzumab is the standard adjuvant therapy for HER2+ breast cancer (von Minckwitz et al. 2017; NCCN 2020). In the HERA trial, the relative reduction in risk of a disease-free event and death were 24% and 26%, respectively, with the addition of 1 year of adjuvant trastuzumab in women with HER2+ early breast cancer (Cameron et al. 2017). In patients with HER2+ disease, an overall 10-year disease-free survival of 69% following 1 year of trastuzumab was reported, and additionally in the HR+ cohort, the 10-year disease-free survival was 72% (Cameron et al. 2017).

2.2.2. Pertuzumab

Pertuzumab, a HER2/neu receptor antagonist, is a dimerized human monoclonal antibody that received approval for use in combination with trastuzumab in the neoadjuvant setting. In 2017, based on results of the APHINITY study (von Minckwitz et al. 2017), pertuzumab, combined with trastuzumab, received approval in the adjuvant treatment setting for patients with HER2+ early breast cancer at high risk of recurrence (pertuzumab package insert, 2013). High-risk patients included patients such as those with HR- or those with node-positive breast cancer. This study demonstrated that the addition of pertuzumab to a trastuzumab-based regimen significantly improves IDFS rates. The 3-year IDFS rates were 94.1% versus 93.2% in the intent-to-treat (ITT) population (hazard ratio=0.81; 95% CI=0.66, 1.00; p=.045). The proportion of IDFS events for patients with node-positive disease was 9.2% (n=139) and 12.1% (n=181) in the pertuzumab and placebo arms, respectively (hazard ratio=0.77, 95% CI=0.62, 0.96). In the cohorts of participants with node-positive disease, the 3-year rates were 92% versus 90.2% (hazard ratio=0.77; 95% CI=0.62, 0.96; p=.02). Higher-risk participants with 4 or more positive-nodes reported a 3-year IDFS of 87.5% versus 84.7% (hazard ratio=0.79; 95% CI=0.59, 1.05) (von Minckwitz et al. 2017).

2.2.3. Trastuzumab Emtansine (T-DM1)

In 2018, results from the KATHERINE study demonstrated that in participants who had residual disease at surgery and after neoadjuvant chemotherapy plus anti-HER2-targeted therapy, 14 cycles of T-DM1, an antibody drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1) resulted in a 50% lower risk of recurrence of invasive disease or death compared to adjuvant trastuzumab alone in patients with HER2+ early-stage breast cancer. The estimated percentage of participants who were free of invasive disease at 3 years was 88.3% in the T-DM1 arm and 77.0% in the trastuzumab arm (hazard ratio for invasive disease or death=0.50; 95% CI=0.39, 0.64; p<.001) (von Minckwitz et al. 2019). Participants with node-positive residual disease remained at higher risk with a reported 3-year IDFS of 83% for T-DM1 versus 67.7% for trastuzumab (hazard ratio for invasive disease or death=0.52; 95% CI=0.38, 0.71) (von Minckwitz et al. 2019). Trastuzumab emtansine in the adjuvant setting is currently approved for use in the US and Europe for patients with residual disease in the resected breast or axilla post-neoadjuvant therapy.

2.2.4. Neratinib

ExteNET showed that 1 year of neratinib, an irreversible pan-HER tyrosine kinase inhibitor (TKI), significantly improves 2-year IDFS after (neo)adjuvant trastuzumab and chemotherapy (either sequentially or concomitantly) in women with HER2+ breast cancer (stratified hazard ratio=0.67; 95% CI=0.50, 0.91; p=.0091) compared to placebo. The 2-year IDFS rate was 93.9% (95% CI=92.4, 95.2) in the neratinib arm and 91.6% (95% CI=90.0, 93.0) in the placebo arm (Chan et al. 2016). In the subset analysis of IDFS, neratinib showed greater benefit to participants with HR+ breast cancer (hazard ratio=0.51; 95% CI=0.33, 0.77) (Chan et al. 2016). In the ExteNET trial, greater and more durable efficacy was observed in the subgroup with HR+ disease who initiated treatment within 1 year of completing trastuzumab. In this subgroup of patients, the absolute invasive disease-free survival (iDFS) benefit of neratinib versus placebo at 5 years was 5.1%, and the absolute OS benefit at 8 years was 2.1% (Chan et al. 2020). Severe diarrhea was a limiting factor with 40% of participants who received neratinib experiencing Grade 3 events and less than 1% experiencing Grade 4 events. Diarrhea led to treatment discontinuation in 17% of participants after a median of 20 days (interquartile range 9-56) (Chan et al. 2016). There is no data to support the use of neratinib post pertuzumab or T-DM1, and it remains unknown if the benefit is maintained for patients who have previously received dual blockade with trastuzumab and pertuzumab.

2.2.5. Endocrine Therapy

The majority of breast cancer diagnosis are known to be HR+. Endocrine therapy represents a key therapeutic strategy for patients with HR+ tumors and has been associated with significant clinical benefits. However, resistance to ET is a common clinical problem in this population which may lead to disease relapse and metastases.

Neoadjuvant or adjuvant ET is indicated in all patients with detectable ER expression (defined as ≥1% of invasive cancer cells), irrespective of the use of chemotherapy (NCCN 2020). The choice of endocrine agent (tamoxifen and/or one of the 3 selective AIs: Anastrozole, letrozole, or exemestane) is primarily determined by the patient's menopausal status. All AIs have shown similar antitumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative setting. Overall, international clinical guidelines (ESMO [Senkus et al. 2015], Saint Gallen International Expert Consensus [Coates et al. 2015]) and NCCN guidelines (2020) for postmenopausal patients, AI should be at least part of ET. In premenopausal patients, standard ET includes tamoxifen with or without ovarian suppression for 5 to 10 years, or an AI for 5 years with ovarian suppression in selected patients at high risk of disease recurrence (that is, pretreated with chemotherapy) based on the TEXT and SOFT studies (Francis et al. 2018). In postmenopausal patients, use of AIs (both nonsteroidal and steroidal) and tamoxifen either sequentially, as monotherapy, or extended therapy for a total duration of 5 to 10 years is a valid option (Francis et al. 2018). Men with breast cancer are treated with AI similarly to postmenopausal women, considering testicular suppression with a gonadotropin-releasing hormone (GnRH) analog (Zagouri et al. 2013).

2.2.6. Abemaciclib

Abemaciclib in combination with ET is approved globally for management of HR+, HER2-negative advanced breast cancer as initial therapy with an AI (MONARCH 3) (Goetz et al. 2017), or after disease progression on prior ET in combination with fulvestrant (MONARCH 2) (Sledge et al. 2017; Sledge et al. 2019). Additionally, abemaciclib is approved by the US Food and Drug Administration (FDA) as monotherapy treatment for endocrine refractory disease in patients with HR+, HER2-negative advanced breast cancer (MONARCH 1) (Dickler et al. 2017).

In the monarchE study, an open-label, randomized Phase 3 trial in participants with HR+, HER2-, node-positive, high-risk early breast cancer, the addition of abemaciclib to standard adjuvant ET resulted in a statistically significant improvement in IDFS. Participants with ≥4 positive axillary lymph nodes; 1-3 positive axillary lymph nodes with either histologic Grade 3 and/or tumor size ≥5 cm; or 1-3 positive axillary nodes with Ki-67 index ≥20% in pre-treated breast tissue as measured by a central laboratory were eligible to participate. The addition of abemaciclib resulted in a 25% reduction in the risk of developing an IDFS event relative to ET alone and an absolute improvement of 3.5% in 2-year IDFS rates (Johnston et al. 2020).

Abemaciclib has an acceptable safety profile in the respective patient populations studied in the two Phase 3 trials for advanced breast cancer (MONARCH 2 and MONARCH 3) in combination with ET, the Phase 2 study (MONARCH 1), a monotherapy study, and in a Phase 3 trial for early high-risk breast cancer (monarchE). The safety monitoring and corresponding dose adjustment guidelines used in these clinical studies effectively managed the toxicity profile of abemaciclib. The most frequently reported adverse events (AEs) include: diarrhea, neutropenia, fatigue, nausea, vomiting, abdominal pain, decreased appetite, and anemia. Additionally, other clinically relevant AEs are venous thromboembolic event (VTE, [including pulmonary embolism (PE) and deep vein thrombosis (DVT)]), alanine aminotransferase (ALT) increased, aspartate transaminase (AST) increased, and interstitial lung disease (ILD)/pneumonitis.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of abemaciclib may be found in the Investigator's Brochure, Participant Information Leaflet, Package Insert, and/or Development Safety Update Report or Summary of Product Characteristics.

More detailed information about the known and expected benefits and risks of standard of care ETs, such as tamoxifen, anastrozole, letrozole, exemestane, and GnRH agonists, may be found in the respective Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

2.3.1. Risk Assessment

The risk assessment table below describes the risk assessment associated with abemaciclib. Since this study is a blinded study (abemaciclib plus ET versus placebo plus ET), it is unknown if all participants will experience any of these risks.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Abemaciclib		
Grade ≥3 Diarrhea	• In MONARCH 2 and MONARCH 3 studies, diarrhea of any grade was observed in 81%-86% of abemaciclib-treated participants, and Grade ≥3 diarrhea was observed in 9%-13% of abemaciclib-treated participants. • In monarchE, diarrhea of any grade was observed in 83% of abemaciclib-treated participants, and Grade ≥3 diarrhea was observed in 8% of abemaciclib-treated participants. • Grade ≥3 diarrhea is considered a key risk based on frequency of occurrence, severity, and potential limited tolerability.	• Investigators should evaluate prior history including 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 prior to participant inclusion into study. • Instruct participants to initiate anti-diarrheal therapy at first sign of loose stools, increase oral fluid intake, and notify the investigator. • Dose modifications and discontinuation of blinded study drug as per guidance provided in protocol table for management of diarrhea (See Section 6.6).
Grade ≥3 Neutropenia	• Neutropenia of any grade occurred in 41%-46% of abemaciclib-treated participants in MONARCH 2 and MONARCH 3 studies. Grade ≥3 neutropenia occurred in 21%-27% of abemaciclib-treated participants. Median time to onset of neutropenia was 11-15 days. • Neutropenia of any grade occurred in 45% of abemaciclib-treated participants in monarchE. Grade ≥3 neutropenia occurred in 19%. • Grade ≥3 neutropenia is considered a key risk based on frequency of occurrence, severity, and the potential complication of serious and life-threatening/fatal infection.	• Inclusion criterion of absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L. • Laboratory monitoring of complete blood count every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. • Dose modifications and discontinuation of blinded study drug as per guidance provided in protocol table for management of hematological toxicity (see Section 6.6).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Interstitial Lung Disease (ILD)/Pneumonitis	• Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in participants treated with abemaciclib and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of abemaciclib-treated participants had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. • In monarchE, 2.7% of abemaciclib-treated participants had ILD/pneumonitis of any grade, and 0.4% had Grade ≥3. • ILD/pneumonitis is included as a key risk based on severity of the condition, lack of predictability, and association with significant morbidity and mortality.	• Investigator should assess for preexisting and active symptoms for ILD/pneumonitis and severe dyspnea at rest or requiring oxygen therapy prior to participant inclusion into study. Patients with such preexisting conditions or ongoing symptoms associated with ILD/pneumonitis are excluded from participation. • Monitor for symptoms, such as hypoxia, cough, dyspnea, or radiologic changes (interstitial infiltrates) indicative of ILD. • Dose modifications and discontinuation of blinded study drug as per guidance provided in protocol table for management of ILD/pneumonitis (Section 6.6).
Grade ≥3 ALT increased	• In MONARCH 2 and MONARCH 3 studies, Grade ≥3 increase in ALT was observed in 4% to 6% of abemaciclib-treated participants. In MONARCH 3, Grade ≥3 increases in ALT (6% versus 2%) were reported in the abemaciclib and placebo arms, respectively. In MONARCH 2, Grade ≥3 increases in ALT (4% versus 2%) were reported in the abemaciclib and placebo arms, respectively. • In monarchE, Grade ≥3 increases in ALT (2.5% vs 0.6%) were reported in the abemaciclib vs ET alone arms, respectively. • ALT elevations (hepatic laboratory results) ≥5×ULN and ≥10×ULN were reported with a higher incidence with the abemaciclib plus ET arm than with ET alone: MONARCH 3, 5.9% vs 1.9% and 1.24% vs 0.63%, respectively; MONARCH 2, 4.4% vs 0.9% and 2.3% vs 0.9%, respectively.	• Inclusion criterion of adequate hepatic function defined as total bilirubin ≤1.5×ULN and ALT and AST ≤3.0×ULN. • Laboratory monitoring of liver function tests (LFTs) every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. • Dose modifications and discontinuation of blinded study drug as per guidance provided in protocol table for management of ALT increased (see Section 6.6). • Additional risk minimization measure: Selected laboratory testing in the event of a treatment-emergent hepatic abnormality (Appendix 5, Section 10.5).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Median time to onset of Grade ≥3 ALT elevation was 57 days in MONARCH 2 and 61 days in MONARCH 3. Median time to resolution of ALT elevation was 14 days in both studies. Grade ≥3 increased ALT is included as a key risk based on severity of the condition, potential association with hepatic synthetic dysfunction, and the requirement to discontinue abemaciclib in response to the event.	
Venous Thromboembolic Events (VTE)	• In MONARCH 2 and MONARCH 3 studies, VTE was observed in 5% of participants treated with abemaciclib combined with ET (either AI or fulvestrant), and in 0.9% of participants treated with ET plus placebo. • In monarchE, VTE (all grades) was observed in 2.4% of participants treated with abemaciclib combined with ET (either tamoxifen or AI). • VTE is included as a key risk based on severity of the conditions, lack of predictability, and potentially significant clinical complications, including fatal outcomes.	• Exclusion of participants with a history of VTE (for example, DVT of the leg or arm and/or pulmonary embolism) from study. • Monitor for symptoms and signs of DVT and pulmonary embolism and treat as clinically indicated. • Suspend dose and treat as clinically indicated. • Blinded study drug may be resumed when participant is clinically stable (Section 6.6).

Abbreviations: AI = aromatase inhibitor; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDK4/6 = cyclin-dependent kinases 4 and 6; DVT = deep vein thrombosis; NSAI = nonsteroidal aromatase inhibitor; ULN = upper limit of normal.

2.3.1.1. Study Intervention

This was initially a randomized, double-blinded, Phase 3 study of abemaciclib plus ET versus placebo plus ET in adult participants with high-risk, HR+, HER2+ early breast cancer who had completed standard adjuvant HER2-targeted therapy. Abemaciclib has an acceptable safety profile in the respective participant populations studied in the three Phase 3 trials (MONARCH 2, MONARCH 3, and monarchE) in combination with ET and the Phase 2 monotherapy study (MONARCH 1). The safety monitoring and corresponding dose adjustment guidelines used in these clinical studies effectively managed the toxicity profile of abemaciclib.

The original design of the control arm was based on current standard medical practice, ethical standards, and the statistical analysis plan (SAP). Using an appropriate concurrent placebo-control arm was intended to enable direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects.

The rationale of using ET plus placebo as a control arm was because ET is currently the standard of care in this population and the use of a double-blind and placebo control minimizes the future assessment of bias.

After approval of amendment (d), and according to local regulations, participants who are on study treatment will be unblinded and enter the Continued Access period and follow the Continued Access SoA (Section 1.3). If the investigator determines that continuation of abemaciclib may offer potential benefit to participants receiving study treatment, participants may continue to receive study treatment in the Continued Access period for a maximum of 26 cycles until any of the criteria for discontinuation are met (Section 7.1). Investigators will perform standard procedures and tests for breast cancer surveillance and management. The choice and timing of the tests will be at the investigator's discretion. The Sponsor will not routinely collect the results of these assessments unless they provide source documentation for an AE. Participants receiving placebo will be discontinued.

2.3.1.2. Study Procedures

Venipuncture to obtain laboratory data is a common clinical practice with low risks of bleeding, vascular or soft tissue injury, and infection (Buowari 2013). Radiologic guidelines for detection of recurrent disease include commonly used imaging modalities. Risks include low levels of radiation exposure and allergic reactions to intravenous contrast (Sammet 2016; Garcia et al. 2017). The investigator will select the most appropriate imaging study for the participant, keeping in mind those potential risks.

2.3.2. Benefit Assessment

Based on the efficacy and safety outcomes in three Phase 3 studies, 2 of which were in HR+, HER2-negative mBC, and 1 large study in HR+, HER2-negative early breast cancer, the use of abemaciclib in high-risk HR+, HER2+ early breast cancer was warranted to justify the study meet the unmet need in this patient population. Details are provided in Sections 2.1 and 2.2.

2.3.3. Overall Benefit: Risk Conclusion

The key risks associated with abemaciclib and other approved CDK4 and CDK6 inhibitors are well known. Health care professionals involved in the care of cancer patients are familiar with the management of these risks. Additionally, the proposed language and guidance detailed in the protocol are considered sufficient for managing and mitigating the key risks.

The study was determined to be no longer feasible due to slow accrual and changes in the treatment landscape for HER2+ breast cancer that are anticipated to improve patient outcomes and diminish the unmet need; therefore, enrollment was terminated 03 February 2022. As of

amendment (d), investigators and participants will be unblinded so that they may make informed decisions regarding continued participation in the trial.

Overall, given the current unmet medical need in the proposed study population and the well-understood AE profile of abemaciclib and the required study procedures, participants randomized to abemaciclib who are deemed, by their investigator, to have potential benefit and who wish to continue the study will be allowed to remain on study.

3. Objectives and Endpoints

Upon approval of amendment (d), the objectives and endpoints in Section 3.1 will be used in place of the objectives and endpoints in this section.

Objectives	Endpoints
Primary	
• To compare the efficacy of abemaciclib plus physician's choice ET versus placebo plus physician's choice ET in the study population.	• IDFS as defined by the STEEP System (Hudis et al. 2007)
Secondary	
• To compare the efficacy of abemaciclib plus ET versus placebo plus physician's choice ET in the study population.	• OS • DRFS • Incidence of CNS metastases as the first site of disease recurrence
• To assess the safety profile of abemaciclib plus physician's choice ET versus placebo plus ET in the study population.	• Safety, including but not limited to TEAEs, SAEs, hospitalizations, clinical laboratory tests, vital signs, and physical examinations
• To evaluate participant-reported symptoms, function and global health status/QOL (EORTC QLQ-C30)	• To compare EORTC QLQ-C30 scales between treatment arms
• To evaluate health status in the study population to inform decision modeling for health economic evaluation using the EQ-5D 5L.	• The EQ-5D 5L the index score and the single-item health status measure
• To evaluate the PK of abemaciclib.	• Abemaciclib concentrations
[redacted]	

Objectives	Endpoints
CCI	

Abbreviations: AE = adverse event; CNS = central nervous system; CCI EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30; EQ-5D 5L = EuroQOL 5 Dimension 5 Level; ET = endocrine therapy; CCI IDFS = invasive disease-free survival; OS = overall survival; PK = pharmacokinetics; CCI SAE = serious adverse event; TEAE = treatment-emergent adverse events.

[a] The 2 most common participant-felt symptoms from each monarchE treatment arm per Johnston et al. 2020.

3.1. Objectives and Endpoints as of Amendment (d)

Objectives	Endpoints
To monitor the safety of abemaciclib plus physician's choice ET in the study population.	AEs and SAEs per CTCAE v5.0

Abbreviations: AEs = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; SAEs = serious adverse events

4. Study Design

4.1. Overall Design

The eMonarcHER Study was initially a Phase 3 multicenter, randomized, double-blinded, placebo-controlled trial in participants with high risk, node-positive, HR+, HER2+ early breast cancer who had completed adjuvant HER2-targeted therapy. Approximately 2450 participants were planned to be enrolled in a 1:1 randomization with participants assigned to blinded study drug (either the abemaciclib or placebo treatment arm) plus ET. Blinded study drug was to have been given for up to 26 cycles, approximately 2 years, or until evidence of disease recurrence or another discontinuation criterion was met, whichever occurred first.

Endocrine therapy was to have been taken as prescribed during the on-study intervention period (approximately 2 years). After the on-study intervention period, standard adjuvant ET was to have continued 3 to 8 additional years, for a total duration up to 10 years, if deemed medically appropriate. Standard approved adjuvant ET was per physician's choice (such as tamoxifen or an AI, with or without ovarian function suppression per standard practice). Adjuvant treatment with fulvestrant was not allowed at any time during the study.

However, the study was ultimately determined to be no longer feasible due to slow accrual and changes in the treatment landscape for HER2+ breast cancer that are anticipated to improve patient outcomes and diminish the unmet medical need; therefore, enrollment was terminated.

After approval of amendment (d), and according to local regulations, participants who are on study treatment will be unblinded. If the investigator determines that continuation of abemaciclib may offer potential benefit to participants receiving study treatment, participants may continue to receive study treatment in the Continued Access period for a maximum of 26 cycles until any of the criteria for discontinuation are met (Section 7.1). Participants receiving placebo will be discontinued.

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.3. Justification for Dose

Abemaciclib

In patients with HR+, HER2-negative mBC, abemaciclib is given orally at 150 mg twice daily in combination with nonsteroidal AIs (anastrozole or letrozole) or fulvestrant. This recommended starting dose is based on the pivotal Phase 3 studies, MONARCH 2 and MONARCH 3, in which the 150 mg twice daily dose exhibited acceptable safety and tolerability, and significant improvement in PFS. Dose adjustments (reductions and omissions) were permitted for tolerability.

In the pivotal Phase 3 study monarchE, participants with HR+, HER2-negative early breast cancer also received 150 mg twice daily abemaciclib, in combination with standard adjuvant ET. This study demonstrated statistically significant improvement in IDFS and acceptable safety and tolerability. A minimum separation of 6 hours between doses was employed in monarchE to

allow maximal absorption between doses. As previously, dose adjustments (reductions and omissions) were permitted for tolerability.

Therefore, in eMonarcHER, abemaciclib will be administered orally at 150 mg twice daily (with at least approximately 6 hours between doses) in combination with ET with dose adjustments as needed for tolerability.

Standard Adjuvant Endocrine Therapy

In MONARCH 3 and Study I3Y-MC-JPBH it was established that abemaciclib does not affect the concentrations of anastrozole, letrozole, tamoxifen, or exemestane. Therefore, standard adjuvant ET will be administered per label or local guidelines at the recommended dose.

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 Continued Access SoA (Section 1.3.1) for the last participant in the trial globally.

5. Study Population

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

Enrollment to the study stopped on 03 FEB 2022. As of amendment (d) all patients enrolled into the study will be unblinded.

5.1. Inclusion Criteria

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

Age

1. Male or female participant must be ≥18 years of age inclusive, at the time of signing the informed consent (or of an acceptable age according to local regulations, whichever is older).

Type of Participant and Disease Characteristics

2. The participant has confirmed HR+, HER2-positive (HER2+), early invasive breast cancer without evidence of disease recurrence or distant metastases per STEEP criteria in Appendix 8 (Section 10.8).
    a. To fulfill the requirement for HR+ disease by local testing on primary disease specimen, tumor must be ER or progesterone receptor (PgR) positive defined by immunohistochemistry (IHC) according to American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for hormone receptor testing (Hammond et al. 2010).
    b. To fulfill the requirement of HER2+ disease by local testing on primary disease specimen, tumor must be HER2+ according to ASCO/CAP guidelines for HER2 testing (Wolff et al. 2018).
    c. Participants with bilateral breast cancer (confirmed pathologic diagnosis of invasive tumors in both breasts simultaneously or within 6 months of each other) or multi-focal disease can be eligible if all lesions tested are HR+, at least 1 lesion is HER2+, and adequate surgery has been performed in the affected breast(s) (see inclusion criterion [3]). The Lilly Clinical Research Physician or Clinical Research Scientist (CRP/CRS) must be consulted for all cases of bilateral breast cancer.
3. The participant must have undergone definitive surgery of the primary breast tumor(s).
    a. With the exceptions described below, the margins of the resected specimen must be histologically free of tumor (either invasive or ductal carcinoma in situ [DCIS]). If tumor was still present at the resected margin, the participant must have undergone re-excision or mastectomy. NOTE: participants with margins positive for LCIS are eligible without additional resection.

b. Participants who, after mastectomy or wide local excision, had microscopic positive margins where the deep margin abutted the pectoralis fascia, may be eligible if they received chest wall radiation per local guidelines prior to study entry.

c. Participants with positive anterior margins may be eligible if there was no residual gross disease and they received radiation therapy per local guidelines.

d. If surgical excision of supraclavicular or internal mammary nodes is not feasible, residual nodes should be irradiated per local guidelines.

4. Participants must have high-risk disease as defined by one of the following criteria:

   a. Those who received neoadjuvant chemotherapy along with HER2-targeted treatment must have

      i. residual disease in at least 1 axillary lymph node or
      ii. a residual tumor ≥ 5 cm, or
      iii. a residual tumor of any size that has direct extension to the chest wall and/or skin (ulceration or skin nodules).

   b. Those who had definitive surgery prior to systemic therapy and completed adjuvant chemotherapy along with HER2-targeted therapies (trastuzumab and pertuzumab) must have

      i. tumor involvement in ≥4 ipsilateral axillary lymph nodes, or
      ii. tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) and
         1. histological Grade 3, or
         2. primary invasive tumor size of ≥ 5 cm on pathological evaluation.

   NOTE REGARDING TUMOR SIZE: Tumor measurement on pathological evaluation. If tumor size is needed to meet eligibility criteria, participants with multifocal/multicentric tumors may be eligible based on the sum of diameters of the individual lesions following discussion with the Lilly CRP/CRS.

   NOTE REGARDING LYMPH NODE INVOLVEMENT: Microscopic tumor involvement is allowed if the tumor deposit measures a minimum of 0.2 mm. Isolated tumor clusters less than 0.2 mm do not meet criteria. Ipsilateral internal mammary and supraclavicular lymph nodes are allowed, but do not count as axillary lymph nodes.

   NOTE ON HISTOLOGY GRADE: Defined by a combined score per the modified Bloom-Richardson grading system (Elston and Ellis 1991), also known as the Nottingham scale, or equivalent following discussion with the Lilly CRP/CRS.

5. Participants must be randomized within 20 months of primary breast cancer surgery.

6. Participants have completed approximately 9 to 20 months of standard HER2-targeted therapy. The total duration of HER2-targeted therapy may include combination of neoadjuvant and adjuvant treatments.

   Eligible adjuvant HER2-targeted regimens include:

   a. For patients treated with neoadjuvant chemotherapy and HER2-targeted therapy, a minimum of 4 cycles of T-DM1 in the adjuvant setting.

      NOTE: Participants may have received up to approximately 6 cycles of adjuvant trastuzumab prior to initiation of T-DM1. Additionally, participants may have switched to trastuzumab-based therapy (monotherapy or in combination with other HER2-targeted therapies) after 4 cycles of T-DM1.

   b. For patients who had definitive surgery prior to systemic therapy, a minimum of 4 cycles of adjuvant pertuzumab with trastuzumab.

7. Participants must be randomized within 12 weeks of completion of adjuvant HER2-targeted therapy.

8. Participants may have received ET (such as tamoxifen or AI) concomitantly with their standard adjuvant HER2-targeted therapy as per physician's choice and may have continued with up to 12 weeks single-agent ET after the completion of HER2-targeted therapy prior to randomization.

   NOTE: Use of GnRH analogues for ovarian suppression is not considered ET for the purposes of this criterion.

9. Have received a minimum of 4 cycles of chemotherapy in either the neoadjuvant or adjuvant setting per standard of care.

10. Have a performance status (PS) of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982).

11. The participant is able to swallow oral medications.

12. Have tumor tissue from breast (preferred) or lymph node for exploratory biomarker analysis available prior to randomization.

    NOTE: Sites should confirm the availability of tumor tissue for exploratory analysis (Section 8.8 and Section 1.3.2) with the pathological laboratory prior to randomization. The lack of tumor tissue in regions where regulations do not permit tissue collection does not constitute a protocol violation and participants may still participate.

13. Participants must have discontinued previous treatments for cancer and recovered from the acute effects of therapy (i.e., Grade ≤1), except for residual alopecia or Grade ≤2 peripheral neuropathy. The washout period from prior treatment to randomization is shown below:

Previous Treatment	Length of Time Prior to Randomization
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥21 days or ≥5 half-lives, whichever is shorter from last dose received
Adjuvant HER2-targeted agents: pertuzumab, trastuzumab, or T-DM1	A washout period of at least ≥21 days is required between last dose of antibody treatment
Exogenous reproductive hormone therapy for purposes other than early-breast cancer (eBC) treatment (for example, birth control pills, hormone replacement therapy, or megestrol acetate). Note, this does NOT apply to ET (tamoxifen or AI) being administered as part of adjuvant therapy for eBC (see IC#8)	≥5 half-lives from last dose received
Radiotherapy	
Adjuvant radiotherapy	≥14 days
Major surgery	≥28 days
Minor surgery, excluding biopsy	≥14 days

14. Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	$\geq 1.5\times10^9$/L
Platelets	$\geq 100\times10^9$/L
Hemoglobin	≥8 g/dL
Note: Transfusions to increase a participant'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 intervention. If a participant receives transfusions, erythropoietin, or G-CSF therapy ≥14 days prior to the first dose, the hematologic criteria listed above must be met following the 14-day window and prior to the first dose of study therapy.	
Hepatic	
Total bilirubin	≤1.5×ULN Participants 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.

Sex

15. Male and/or female

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

a. Male participants:

Male participants are eligible to participate if they agree to refrain from donating sperm while taking blinded study drug. The use of contraception in male participants is not required.

b. Female participants:

1. Women of childbearing potential (WOCBP) who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or refrain from sexual intercourse with males during study intervention period. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Otherwise, WOCBP participating must agree to use one highly effective method (less than 1% failure rate) of contraception while taking blinded study drug and for 3 weeks after the last dose of blinded study drug.

   Women of childbearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine or serum pregnancy test within 24 hours prior to exposure.

3. Women not of childbearing potential may participate and include those who are:
   A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis; or
   B. post-menopausal – defined as either
      i. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone ≥40 mIU/mL; or
      ii. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
      iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Informed Consent

16. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), 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 apply:

Medical Conditions

17. Participant has breast cancer with any of the following features:

    - Disease recurrence or distant metastatic disease (including contralateral axillary lymph nodes)
    - Pathological complete response (pCR) from any prior early breast cancer treatments. Participants are required to have residual primary tumor and/or lymph node disease at the time of definitive surgery as indicated in inclusion criteria.
    - Inflammatory breast cancer.

      NOTE: Inflammatory carcinoma should not apply to a participant with neglected locally advanced breast cancer presenting late in the course of their disease (American Joint Committee on Cancer [AJCC] staging system for breast cancer 8th edition, Hortobagyi et al. 2017). The investigator should consult with the Lilly CRP/CRS regarding eligibility of participants with neglected inflammatoid disease.
    - Participants with a history of previous breast cancer, with the exception of ipsilateral DCIS treated by locoregional therapy alone ≥5 years ago. Participants with a history of contralateral DCIS treated by local regional therapy at any time may be eligible.

18. Participants with a history of any other cancer are excluded, unless in complete remission with no therapy for a minimum of 5 years from the date of randomization.

- For participants with a history of other non-breast cancers within 5 years from the date of randomization and considered to be very low risk of recurrence per investigator's judgment (for example, papillary thyroid cancer treated with surgery), eligibility is to be discussed with the Lilly CRP/CRS.
- Participants with history of non-melanomatous skin cancer that was treated with curative intent, or appropriately treated carcinoma in situ (CIS) of cervix, bladder, colon are eligible.

19. Females who are pregnant or lactating.
20. Participants with significant clinical cardiac abnormalities (e.g., clinical heart failure, unstable angina, or ejection fraction (EF) <35%) are excluded. This should be documented at the completion of adjuvant HER2 targeted therapy.
21. The participant has serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment, [for example, estimated creatinine clearance <30 mL/min], 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, ulcerative colitis, or a preexisting chronic condition resulting in clinically significant diarrhea).
22. Any participant with a history of VTE (for example, DVT of the leg or arm and/or PE) will be excluded. This includes a history of catheter-associated thromboses.
23. Any participant that has known active systemic infections (for example, bacterial infection requiring IV antibiotics at time of initiating study intervention, fungal infection or detectable viral infection requiring systemic therapy) is not eligible.
    a. Participants with uncontrolled human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) defining illness are not eligible. Participants with known HIV infection and CD4+ T-cell (CD4+) counts ≥350 cells/µL are eligible.
    b. Participants with hepatitis B are not eligible unless hepatitis B virus (HBV) viral load is below the level of quantification.
    c. Participants with known hepatitis C are not eligible unless they have completed curative anti-viral therapy and hepatitis C virus (HCV) viral load is below the level of quantification.
    d. Screening for HIV, coronavirus disease 2019 (COVID-19), Hepatitis B or Hepatitis C is not required.

Prior/Concomitant Therapy

24. The participant has previously received treatment with any CDK4 and 6 inhibitor.

25. The participant has received prior adjuvant treatment with immunotherapy, tucatinib, neratinib, any investigational HER2-directed therapy, or T-DXd (DS8201) for treatment of breast cancer. Prior exposure with these agents during neoadjuvant treatment will be allowed.
26. The participant has previously received ET (i.e., tamoxifen, raloxifene or AI) for breast cancer prevention (without diagnosis of breast cancer).
27. The participant is receiving any additional chemotherapy, anticancer ET, or HER2-targeted therapy beyond standard of care at study enrollment. This includes concurrent exogenous reproductive hormone therapy (for example, birth control pills, hormone replacement therapy, or megestrol acetate). Note: Topical vaginal estrogen therapy is permitted if all other non-hormonal options are exhausted.
28. Exclusion criterion [28] has been deleted.
29. Participants with known or suspected hypersensitivity reactions or intolerance to abemaciclib or to any of the excipients (e.g., lactose) should not take abemaciclib unless deemed appropriate by the investigator.

Prior/Concurrent Clinical Study Experience

30. Have participated, within the last 30 days; (3 months for studies conducted in the United Kingdom [UK]), in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) and 3 months for studies conducted in the UK should have passed. Exceptions will be considered on a case-by-case basis by the sponsor CRP/CRS.

5.3. Lifestyle Considerations

Participants should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to the effect on cytochrome P450 (CYP)3A4. Investigators are expected to review the appropriate product label for the standard endocrine therapy treatment that he/she has proposed for the participant.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number. Individuals may be re-screened up to one time. The interval between a screen failure and the start of re-screening must be at least 2 weeks. When re-screening is performed, the individual must sign a new ICF. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol designated screening period does not constitute rescreening.

Potential reasons for rescreening:

- Participants who have become eligible to enroll in the study as the result of a protocol amendment.
- Participants status has changed such that the eligibility criterion that caused the participant to screen fail would no longer cause the participant to screen fail again.
- Participants 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, or child illness).

Participants who decide to discontinue study intervention after randomization may not be rescreened or resume study intervention.

As of 03 February 2022, no new patients will be screened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol during the on-study intervention period (up to 26 cycles).

6.1. Study Intervention(s) Administered

Arm	Arm A (experimental)		Arm B (control)	
Intervention	Abemaciclib	ET	Placebo	ET
Dose	150 mg (3, 50 mg tablets)	Standard adjuvant ET of physician's choice	3 placebo tablets	Standard adjuvant ET of physician's choice
Schedule	BID		BID	
Route	PO		PO	

Abbreviations: BID = twice a day, at least approximately 6 hours apart; ET = endocrine therapy; PO = by mouth; mg = milligrams.

Abemaciclib/Placebo:

Initially, assignment to either abemaciclib or placebo was blinded to investigators and participants. Abemaciclib/placebo, hereafter described as "blinded study drug" will be administered at a starting dose of 150 mg twice daily and it is provided as 50-mg tablets. Participants were to have received blinded study drug up to 26 cycles (approximately 2 years). Blinded study drug was to have been taken twice daily (with at least approximately 6 hours separating doses) at the same time each day with a glass of water. Participants were instructed to swallow tablets whole and not chew or crush.

As of amendment (d), investigators and participants will be unblinded. Participants receiving placebo will be discontinued. See Section 2.3.1.1.

Endocrine therapy:

Initially, the investigator's choice of standard of care ET was planned for up to 26 cycles (approximately 2 years) on study and then up to 10 years total duration, as medically indicated. The investigator was to refer to the product label for administration of standard of care ET of choice. A switch to another standard ET was allowed as per the investigator's discretion (Section 10.8). Adjuvant treatment with fulvestrant was not allowed at any time during the study.

As of amendment (d), ET choice and duration remains at the discretion of the investigator.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

3. The investigator or authorized study personnel is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Initially, this was a randomized, double-blind, placebo-controlled study. Participants who meet all criteria for enrollment were randomly assigned to Arm A (abemaciclib plus ET) or Arm B (placebo plus ET). Approximately 2450 participants were anticipated to enroll and be randomized 1:1 between the 2 arms using the following stratification factors:

- Prior neoadjuvant systemic therapy: yes vs no
- Menopausal status: premenopausal vs postmenopausal (including males) (menopausal status to be determined by investigator and based upon the participant's status at the time of diagnosis)
- Region: North America/West Europe vs Asia vs Other

All randomized participants were centrally assigned to treatment arms using an Interactive Web Response System (IWRS). Study intervention was dispensed at the study visits summarized in the SoA (Section 1.3).

Following the approval date of amendment (d), and subject to local guidelines, participants and investigators will be unblinded. See Section 6.3.4. Efficacy will no longer be an endpoint.

6.3.1. Unblinding at Interim Analyses

Beginning with amendment (d), no interim analyses are planned.

6.3.2. Emergency Unblinding

Upon approval of amendment (d), and subject to local guidelines, participants and investigators will be unblinded (see Section 6.3.4) without designation as emergency unblinding; therefore, considerations for emergency blinding are no longer applicable. Unblinding as of amendment (d) does not require participant discontinuation from the trial, if the participant is receiving abemaciclib. If the participant is receiving placebo, they will discontinue from the trial after the final short-term follow-up visit is completed.

6.3.3. Inadvertent Unblinding

Upon approval of amendment (d), and subject to local guidelines, all participants and investigators will be unblinded (see Section 6.3.4) and therefore considerations for inadvertent blinding are no longer applicable. Intentional unblinding after amendment (d) does not require participant discontinuation from the trial if the participant is receiving abemaciclib. If the participant is receiving placebo, they will discontinue from the trial after the final short term follow up visit is completed.

6.3.4. Amendment (d) Unblinding

Upon approval of amendment (d), and subject to local regulations, participants will be unblinded. Unblinding will not necessitate protocol discontinuation if the participant is receiving abemaciclib. If the patient is receiving placebo, they will discontinue from the trial after the final short term follow up visit is completed.

6.4. Study Intervention Compliance

Initially, when participants self-administered study intervention(s) at home, compliance was assessed as per the SoA (Section 1.3). Compliance for blinded study drug was assessed by counting dispensed and returned tablets and this was to be recorded in the source documents and case report form (CRF). Compliance for ET was assessed by direct questioning and recorded in the source documents and CRF.

A record of the number of blinded study drug tablets dispensed was maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions were to have been recorded in the CRF.

A participant must have taken ≥75% of the planned doses to be deemed compliant. Similarly, a participant may have been considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study drug in a cycle.

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

As of amendment (d), the study will not evaluate compliance.

6.5. Concomitant Therapy

Initially, all concomitant medications were to have been recorded throughout the on-study intervention period and through short-term follow-up. However, as of amendment (d), use of concomitant medications will not be collected.

In general, the list of prohibited medications that affected participant eligibility or participation in the study were limited to ET for breast cancer prevention, concurrent exogenous reproductive hormone therapy, and recent experimental treatment in a clinical trial. Replacement hormonal therapy (e.g., thyroid or adrenocorticoid supplementation) were allowed. Exogenous reproductive hormone therapy (for example, birth control pills, hormone replacement therapy, or megestrol acetate) were not allowed; however, topical vaginal estrogen therapy was permitted if all other non-hormonal options were exhausted. Concurrent treatment with standard of care bone-modifying agents (such as bisphosphonates and denosumab) was permitted.

As of amendment (d), concomitant medications were not routinely documented for the Sponsor unless they were associated with an AE. Concomitant medications decisions are at discretion of the investigator.

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 7, Section 10.7). 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) at the discretion of the investigator.

Inducers of CYP3A should be substituted or avoided if possible (Appendix 7, Section 10.7).

Transporter Substrates

At clinically relevant concentrations, abemaciclib inhibits the transporters P-glycoprotein, breast cancer resistance protein, organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K. In vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin and dabigatran, may occur.

6.5.1. Supportive Care

The need for any radiotherapy for treatment of breast cancer will be cause for early discontinuation from the study treatment.

In addition, any disease recurrence or progression requiring other specific antitumor therapy will necessitate early discontinuation from the study treatment. Initially, appropriate documentation for all forms of premedications, supportive care, and concomitant medications were to be captured on the CRF. As of amendment (d), documentation of premedication, supportive care, and concomitant medications will not be captured on the CRF unless necessary to support documentation of a SAE.

Participants should receive full supportive care. The use of granulocyte-colony stimulating factor is permitted based on ASCO (Smith et al. 2015) and ESMO (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).

6.5.2. Supportive Management for Diarrhea in Participants Receiving Blinded Study Intervention

Participants should receive instructions on the management of diarrhea at the initiation of study treatment. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the participant should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Participants should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1 (per Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), blinded study intervention should be suspended until diarrhea is resolved to at least Grade 1.
- When blinded study intervention recommences, dosing should be adjusted as outlined in Section 6.6.1. In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

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

Participants with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid and electrolyte replacement as clinically indicated.

6.6. Dose Modification

Initially, investigators were referred to the following tables for dose modifications for adverse reactions related to blinded study drug. If dose reduction was necessary, the dose was decreased by 50 mg at a time. Blinded study drug was discontinued for participants unable to tolerate 50 mg twice a day, at least approximately 6 hours apart (BID).

As of amendment (d), dose modifications will be at the investigator's discretion, though the modifications below are encouraged.

Blinded Study Drug Dose Modification For Adverse Reactions

Dose Level	Blinded Study Drug Dose
Recommended starting dose	150 mg BID
First dose reduction	100 mg BID
Second dose reduction	50 mg BID
Third dose reduction	Not applicable

Abbreviation: BID = twice a day, at least approximately 6 hours apart.

Blinded Study Drug Dose Modification and Management – Hematologic Toxicities

Monitor complete blood counts prior to the start of blinded study drug therapy, every 2 weeks for the first 2 cycles, and then according to the SoA and as clinically indicated.	
CTCAE Grade	**Blinded Study Drug Dose Modifications**
Grade 1 or 2	No dose modification is required
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2 Dose reduction is not required
Grade 3, recurrent, or Grade 4[a]	Suspend dose until toxicity resolves to ≤Grade 2 Resume at next lower dose
Participant requires administration of a blood cell growth factor	Suspend blinded study drug dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2 Resume blinded study drug at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; SoA = schedule of activities.

[a] 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 preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a participant who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of 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 treatment

Blinded Study Drug Dose Modification and Management – Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide.	
CTCAE Grade	**Blinded Study Drug Dose Modifications**
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. Dose reduction is not required
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures[a]	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose
Grade 3 or 4 or requires hospitalization	

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

[a] 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 preceding event).

Blinded Study Drug Dose Modification and Management – Increased ALT/AST

Monitor ALT/AST prior to the start of blinded study drug therapy, every 2 weeks for the first 2 cycles, and then according to the SoA and as clinically indicated.	
CTCAE Grade	**Blinded Study Drug Dose Modifications**
Grade 1 (>ULN-3.0×ULN) Grade 2 (>3.0-5.0×ULN)	No dose modification is required
Persistent or recurrent[a] Grade 2 or Grade 3 (>5.0-20.0×ULN)	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose
≥Grade 2 (≥3.0×ULN) with total bilirubin >2×ULN, in the absence of cholestasis	Discontinue blinded study drug
Grade 4 (>20.0×ULN)	Discontinue blinded study drug

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; SoA = schedule of activities; ULN = upper limit of normal.

[a] 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 preceding event).

Blinded Study Drug Dose Modification and Management – Interstitial Lung Disease/Pneumonitis

CTCAE Grade	**Blinded Study Drug Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days[a]	Suspend dose until toxicity resolves to baseline or Grade ≤1. Resume at next lower dose.
Grade 3 or 4	Discontinue blinded study drug.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

[a] 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 preceding event).

Blinded Study Drug Dose Modification and Management –Venous Thromboembolic Events)

CTCAE Grade	**Blinded Study Drug Dose Modifications**
Any Grade	Suspend dose and treat as clinically indicated. May resume blinded study drug when participant is clinically stable.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Blinded Study Drug Dose Modification and Management – Nonhematologic Toxicities Excluding Diarrhea, ALT/AST Increased, and ILD/pneumonitis and VTE)

CTCAE Grade	Blinded Study Drug Dose Modifications
Grade 1 or 2	No dose modification is required
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1[a]	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose
Grade 3 or 4	

Abbreviations: ALT = alanine aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; VTE = venous thromboembolic event.

[a] 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 preceding event).

6.6.1. Dose Suspension and Cycle Delay

As of amendment (d), both dose suspension and delays of abemaciclib and ET will be determined by the investigator. If abemaciclib dose hold or suspension exceeds 28 days, consideration of discontinuation is encouraged.

For participants undergoing surgery, the following recommendations should be considered:

- Minor Surgeries:
  - Abemaciclib should be suspended before surgery at investigator's discretion, and for at least 14 days after surgery.
- Major Surgeries:
  - Abemaciclib should be suspended for at least 7 days before surgery, and for at least 21 days after surgery.

For both minor and major surgeries, investigators should treat as clinically indicated and closely monitor any signs of infection or healing complications. Consider monitoring neutrophils and platelets before surgery and before resuming blinded study drug. The scars should be aseptic and healing process be reasonable before resuming blinded study drug.

6.7. Intervention after the End of the Study

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

6.7.1. Study Completion Definition

As of amendment (d), the study will be considered complete when the final participant discontinues from the study or completes 26 cycles of abemaciclib and a final short-term follow-up visit or is declared lost to follow-up.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants will remain on treatment unless/until a discontinuation criterion is met, at which point study intervention is permanently discontinued. Participants will then enter the follow-up period with follow-up procedures performed as shown in the SoA section (Section 1.3).

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

- The participant becomes pregnant while receiving study intervention
- The participant is significantly noncompliant with study procedures and/or treatment
- Disease recurrence
- Unacceptable toxicity
- The participant, for any reason, requires treatment from another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study intervention will occur prior to introduction of the new agent
- Enrollment in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- If the investigator decides that the participant should be discontinued from the study
- After the completion of 26 cycles (approximately 2 years) of abemaciclib
- Upon unblinding, the participant is determined to have been receiving placebo.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

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

If possible, at the time of discontinuation, a short-term follow-up visit (V801) should be conducted according to the SoA.

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

As of amendment (d), any participant determined to have been inadvertently enrolled will be discontinued from the study unless their continuation had previously been approved by the

Sponsor. Safety follow-up is as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol

For sites located in the UK, refer to Appendix 6 (Section 10.6) for country-specific discontinuation guidelines.

7.2.2. Discontinuation after Amendment (d)

Upon approval of amendment (d), the participant or investigator may request discontinuation from the study. Participants randomized to the placebo arm will be discontinued from the study. Participants randomized to the abemaciclib arm may remain on the study if deemed appropriate by the investigator and the participant wishes to continue.

7.3. Lost to Follow up

A participant 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 or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor 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.

8.1. Efficacy Assessments

8.1.1. Imaging and Recurrence Assessment

All applicable imaging will be done locally. No central imaging assessments will be performed during the study. For details, see SoA (Section 1.3).

Following approval of amendment (d), imaging decisions for disease recurrence should continue per the investigator's judgment and according to routine standard practice. Efficacy data will not be collected, and safety will be the primary endpoint.

8.1.2. Appropriateness of Assessments

With the termination of enrollment and changes to primary endpoint, no additional efficacy data will be collected as of amendment (d).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). For each participant, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3). After approval of amendment (d), clinical laboratory test selection, timing and frequency are at the discretion of the investigator.

Results from any clinical laboratory test analyzed by a central laboratory (refer to Section 10.2, Appendix 2) will be provided to investigative sites by Lilly or its designee. Upon approval of amendment (d), central labs will not be collected.

Given the nonclinical safety findings related to eye (cataract, retinal atrophy, corneal inflammation) and testes (benign adenomas and impairment of fertility), during each clinic or phone visit, participants will be monitored for signs and symptoms of visual impairment and testicular anatomical changes. Refer to Section 8.3 for details on the recording of AEs.

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

8.2.1. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
    - Upon approval of amendment (d), clinical laboratory test selection, timing and frequency are at the discretion of the investigator.
- Local laboratory results are only required if the central laboratory results are not available in time for inclusion/exclusion determination, study intervention administration, and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if local laboratory results are used to make a treatment decision, the results must be entered into the CRF. If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (for example, hypertension, neutropenia, etc.) this should be reported in the CRF as an AE. Do not enter the test abnormality; enter the disease, diagnosis, or categorical term.
    - Upon approval of amendment (d), central laboratory samples will not be collected.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
    - Upon approval of amendment (d), clinical laboratory test selection, timing and frequency are at the discretion of the investigator. Laboratory results associated with an AE must be retained as specified above.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or until the completion of Visit 801 should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual, standard collection requirements, and the SoA.

- Upon approval of amendment (d), clinical laboratory assessment is at the discretion of the investigator,

- If laboratory values from nonprotocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then report the information as an AE.

8.2.2. Hepatic Safety Monitoring

Close Hepatic Monitoring and Evaluation

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

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

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator in consultation with the Lilly-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 computed tomography [CT] scan).

Based on the participant's history and initial evaluation results, further testing should be considered, in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), 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 (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, and/or a liver biopsy.

Additional Hepatic Safety Data Collection

Prior to amendment (d), additional safety data should be collected via the CRF if 1 or more of the following conditions occur:

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

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

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

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

Safety data capture in the CRF is not required after approval of amendment (d), however source documents related to AE should be retained.

In all study participants (including after approval of amendment (d))

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

8.2.3. Venous Thromboembolic Events (VTEs)

In the randomized Phase 3 studies in patients with advanced or mBC (MONARCH 2, MONARCH 3 studies) or early breast cancer (monarchE study) treated with abemaciclib in combination with ET, a greater number of patients experienced VTE events in the abemaciclib plus ET arm than in the placebo plus ET arm or ET alone arm. The majority of patients who experienced VTEs were treated with anticoagulants. In the monarchE study, there was a trend towards an increased incidence of VTEs (including PE) in patients receiving tamoxifen as first background ET as compared to AIs. In next the MONARCH 1 study, a greater number of patients experienced VTE events in the abemaciclib plus tamoxifen arm compared with the abemaciclib monotherapy arms. No events of VTE resulted in death or discontinuation of the study treatment, and most patients were treated with LMWH.

Venous thromboembolic events is an adverse drug reaction for abemaciclib. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Venous thromboembolic events have been reported with other CDK4 and CDK6 inhibitors and ET is known to be associated with the occurrence of VTEs. Participants should be monitored for signs and symptoms of DVT and PE and treated as medically appropriate.

8.2.4. Serum Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting glomerular filtration rate (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 (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Dose adjustment (omission, reduction, or discontinuation) should not be based solely on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, a cystatin C measurement may be performed to confirm renal status. Dose alteration should follow the protocol guidance for non-hematological toxicities.

8.2.5. Interstitial Lung Disease (ILD)/Pneumonitis

Interstitial lung disease/pneumonitis is an AESI for abemaciclib. Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in participants treated with abemaciclib.

Ask your participants to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include thoracic imaging, such as high-resolution CT, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Section 6.6.1 for guidance on dose adjustments of blinded study drug for participants with ILD/pneumonitis. Discontinue blinded study drug in cases of Grades 3 or 4 ILD/pneumonitis.

Additional information is available in the Investigator's Brochure.

8.3. Adverse Events and Serious Adverse Events

The investigator will use CTCAE Version 5.0 (National Cancer Institute [NCI] 2018) to assign AE severity grades.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures during the on-study intervention period (up to 26 cycles), or that caused the participant to discontinue the study intervention (see Section 6.7.1).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until completion of Visit 801 (completion of the 26 cycles of study intervention from first dose of blinded study drug or at time of study intervention discontinuation and during short-term follow-up).

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the AE CRF.

All SAES will be reported to the sponsor once the participant has signed the ICF and has received the first dose of study drug. If an SAE occurs after signing the ICF, but prior to

receiving blinded study drug, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures. Reporting and collection of SAEs must continue for 5 years, or until participation in the study has ended, regardless of causality, relatedness, or the arm to which the participant was initially randomized.

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

Investigators are not obligated to actively seek SAEs after conclusion of the 5-year duration after start of study intervention. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2.2). Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure. If a participant becomes pregnant, she will be discontinued from study intervention. The decision to continue in study will be at the participant's and physician's discretion.
- 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 Appendix 4, Section 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Events or Outcomes

Events leading to the clinical outcome of death due to disease recurrence or other endpoints, either invasive disease recurrence, distant disease recurrence, or CNS disease recurrence 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.

8.3.7. Adverse Events of Special Interest

The following AEs are considered to be AESIs for abemaciclib:

- Neutropenia,
- Infections,
- Diarrhea,
- Hepatic events, including increases in AST and ALT,
- VTEs, and
- ILD/pneumonitis.

8.3.8. Product Complaints

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

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

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 3, Section 10.3 of the protocol.

8.3.8.1. Time Period for Detecting Product Complaints

- Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug 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 a drug provided for the study, the investigator will promptly notify the sponsor.

8.3.8.2. 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 email. If email is unavailable, then an alternative should be utilized.

8.3.8.3. 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/treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Obtain a sample for pharmacokinetics (PK) analysis as soon as possible after the overdose has been identified, unless the medical monitor specifies otherwise.
4. 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.

8.5. Pharmacokinetics

Initially, pharmacokinetic (PK) samples were to be collected from approximately 20% of study participants at the visits and times specified in the SoA (Section 1.3.2) to determine the concentrations of abemaciclib and its active metabolites, LSN3106726 (M20) and LSN2839567 (M2).

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

Upon approval of amendment (d), no additional PK collection is planned.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Upon approval of amendment (d), no additional blood samples for genetic analyses will be collected.

8.8. Biomarkers

Upon approval of amendment (d), no additional blood samples for biomarker analyses will be collected.

8.8.1. Plasma and Serum Samples for Biomarker Research

Upon approval of amendment (d), no additional plasma and serum samples for biomarker research will be collected.

8.8.2. Tissue Samples for Biomarker Research

Upon approval of amendment (d), no new participants will be enrolled therefore no additional tissue samples for biomarker research will be collected.

8.8.3. Whole-Blood Sample for Biomarker Research

Upon approval of amendment (d), no additional whole blood samples for biomarker research will be collected.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics

Upon approval of amendment (d), no health economic questionnaires will not be collected.

8.10.1. Patient-Reported Outcomes (PRO)

Upon approval of amendment (d), no further PRO assessment will be collected.

8.10.2. Electronic Participant Daily e-Diary Assessment

Upon approval of amendment (d), PRO assessment will not be collected, and the e-diary portal will be discontinued.

8.10.3. Healthcare Resource Utilization

Upon approval of amendment (d), healthcare resource utilization assessments will not be collected.

9. Statistical Considerations

9.1. Statistical Hypotheses

Treatment of participants with high-risk, node-positive, HR+, HER2+ breast cancer (who have completed adjuvant HER2-targeted therapy) with abemaciclib plus ET will provide a clinically meaningful increase in IDFS over treatment with placebo plus ET.

Upon approval of amendment (d) and permanent closure of the study to enrollment, the sponsor will not evaluate the statistical hypothesis as originally planned.

9.2. Sample Size Determination

Approximately 2450 participants were originally planned to be randomized. At time of closure of the study to enrollment, the total enrollment is anticipated to be approximately 115 patients.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Intent-to-Treat (ITT)	All randomized participants, regardless of whether they took any doses of study intervention, or if they took the correct treatment. Participants will be analyzed according to the treatment group as randomized and not by actual treatment received.
Safety	All randomized participants who received at least 1 dose of any study intervention. Participants will be analyzed according to the first dose of study intervention they actually received, regardless of the arm to which they were randomized.
Pharmacokinetic (PK) Analysis	All randomized participants who received at least 1 dose of study intervention and have baseline and at least 1 postbaseline evaluable PK sample. Pharmacokinetic sampling is planned to occur in 20% of study participants. As of amendment (d), no further PK sampling is planned.

9.4. Statistical Analyses

9.4.1. General Considerations

Upon approval of amendment (d) and permanent closure of the study to enrollment, the sponsor will not evaluate the statistical hypothesis as originally planned, thus Sections 9.4.2, 9.4.3 and 9.4.4 are no longer applicable.

9.4.2. Primary Endpoint(s)

Upon approval of amendment (d), the sponsor will not evaluate the statistical hypothesis as originally planned, thus Section 9.4.2 is no longer applicable.

9.4.3. Secondary Efficacy Endpoint(s)

Upon approval of amendment (d), the sponsor will not evaluate any secondary efficacy endpoints, including overall survival and distant relapse-free survival.

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9.4.5. Safety Analyses

All participants in the safety analysis set in Section 9.3 will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.1 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term will be used in the treatment-emergent computation. Treatment-emergent AEs will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term within SOC.

Safety analyses will include summaries of the following:

- treatment-emergent AEs, including severity and possible relationship to study intervention
- treatment-emergent SAEs, including possible relationship to study intervention
- adverse events leading to dose adjustments
- discontinuations from study intervention due to AEs or death

9.4.6. Other Analyses

9.4.6.1. Participant Disposition

A detailed description of participant 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 participants completing the study, as defined in the SAP, or discontinuing prior to study completion (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.4.6.2. Participant Characteristics

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

9.4.6.3. Concomitant Therapy

As of amendment (d), concomitant therapy will not be collected or reported.

9.4.6.4. Treatment Compliance

As of amendment (d), treatment compliance will not be collected or reported.

9.4.6.5. Extent of Exposure

As of amendment (d), exposure data will not be collected or reported.

9.4.6.6. Post-Study intervention Therapy

As of amendment (d), post-study intervention therapy will not be collected or reported.

9.4.6.7. Subgroup Analyses

As of amendment (d), subgroup analyses will not be reported.

9.4.6.8. Pharmacokinetic and Exposure-Response Analyses

As of amendment (d), PK and exposure-response analyses will not be performed. No additional PK specimens will be collected.

9.4.6.9. Biomarker Analyses

As of amendment (d), biomarker analyses will not be performed or reported. No additional biomarker specimens will be collected.

9.4.6.10. Health Economics Analyses

As of amendment (d), health economic analyses will not be performed or reported. No additional health economic data will be collected.

9.5. Interim Analyses

9.5.1. Interim Analyses for Efficacy/Futility:

Upon approval of amendment (d) the sponsor will not evaluate the statistical hypothesis as originally planned thus there will be no interim efficacy/futility analyses.

9.5.2. Interim Analyses for Safety

Upon approval of amendment (d) the study will no longer be blinded, and an unblinded DMC will not be utilized. The Sponsor will conduct trial level safety reviews of unblinded safety data.

9.6. Data Monitoring Committee (DMC)

Upon approval of amendment (d), there will be no data monitoring committee.

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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
  - Substantial amendments to the protocol will require regulatory authority approval before implementation.
- 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
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement (CTA).

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (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 reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

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

10.1.4. Data Protection

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

10.1.5. 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.

Data

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

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, clinical study report, blank or annotated CRFs will be provided in a secure data sharing environment for up to 2 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 (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant into an instrument (tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

As of amendment (d), eCOA data will not be collected, analyzed, or reported.

Data collected via the sponsor-provided data capture system will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. 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 electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to 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.
- Definition of what constitutes source data can be found in Section 10.1.6 (Data Quality Assurance).

10.1.8. Study and Site Start and Closure

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

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

The study or a study site will be discontinued if the sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

10.1.9. Publication Policy

Results of this study will not be submitted for publication.

10.1.10. Investigator Information

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the laboratory indicated.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for inclusion/exclusion determination, study intervention administration, and/or response evaluation. If a local sample is collected, it is important that the sample for central analysis is obtained at the same time. If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (for example, hypertension, neutropenia, etc.) this should be reported in the CRF as an AE. Do not enter the test abnormality; enter the disease, diagnosis, or categorical term.
- Discrepancies between local and central laboratory results will not be considered protocol deviations when central labs are unavailable and local labs are used to make treatment decisions.
- In circumstances where the sponsor approves local laboratory testing in lieu of central testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations and clinically significant findings should be reported in the CRF as an AE.
- As of amendment (d), monitoring of participants who continue on study treatment will be at the discretion of investigator and should follow prescribing guidelines. Sponsor will not collect results of routine laboratory tests unless these are needed as source verification of an AE.

Investigators must document their review of the laboratory safety results.

Hematology – central laboratory		
• Leukocytes (WBC) • Neutrophils, absolute • Lymphocytes	• Hemoglobin (HGB)	• Hematocrit (HCT) • Platelets (PLT)

Chemistry –central laboratory
Serum concentrations of:

- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Bilirubin, total
- Blood urea nitrogen (BUN) or blood urea
- Calcium
- Chloride
- Creatinine
- Glucose
- Potassium
- Sodium
- Total protein

Cystatin-C - central laboratory as clinically indicated

Hepatic Safety Monitoring – see Section 8.2.2 and Appendix 5 (Section 10.5)

Pregnancy test (for female participants of childbearing potential) – local laboratory

- When a urine pregnancy test is performed, a minimum sensitivity of 25 IU/L or equivalent units of β-hCG is required. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. A serum pregnancy test is required at screening.

Abbreviations: RBC = red blood cell; WBC = white blood cell.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent 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 it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

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

10.3.2. Definition of SAE

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

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

Results in death

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.

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.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by 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 make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

The investigator will use Common Terminology Criteria for Adverse Events (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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator 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 or the SAE coordinator.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE form.

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

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females are considered women not of childbearing potential if

- they have a congenital anomaly such as Mullerian agenesis,
- they are infertile due to surgical sterilization, or
- they are post-menopausal.

Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, tubal ligation.

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

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

1. Postmenopausal female is defined as, women with:
    - 12 months of amenorrhea for women >55, with no need for follicle-stimulating hormone (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 (e.g., oral contraceptives, hormones, GnRH, anti-estrogens, selective ER modulators [SERMs], or chemotherapy that induced amenorrhea)

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY
The choice of the most effective and appropriate contraception method is up to 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 intrauterine devices [IUDs]) is contraindicated, and the effect of progestin-based hormonal contraception remains unclear. The Clinical Trial Facilitation Group has defined highly effective/effective methods of contraception[1]. **Highly Effective Methods Allowed During the Study Include the Following:** • IUD, only hormone-free • Bilateral tubal occlusion • Vasectomized partner[2] • Sexual abstinence[3] Local regulation/guidelines are to be followed with regards 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 2014. Available at: http:hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CFTG_Contraception.pdf.Accessed May 02, 2016.

[2] Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

[3] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including 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 Section 8.3.5. 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.

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

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 8.2.2 for guidance on appropriate test selection.

- **For testing selected, analysis is required to be completed by the Lilly designated central laboratory except for Microbiology.**
- **Local testing may be performed in addition to central testing when required for immediate participant management.**
- **Upon approval of amendment (d), testing is at the discretion of the investigator and will be performed locally**
- **Results will be reported if a validated test or calculation is available.**

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (Quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin IgG (Quantitative)
HAV Total Antibody	Immunoglobulin IgM (Quantitative)
HAV IgM Antibody	Phosphatidylethanol (PEth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

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

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

[a] This is not required if anti-actin antibody is tested.

[b] This is not required if ASMA is tested.

[c] Assayed by investigator-designated local laboratory ONLY; no central testing available.

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

10.6. Appendix 6: Country-specific Requirements

10.6.1. Discontinuation of Inadvertently Enrolled Participants in the United Kingdom

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

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

The informed consent process (Section 10.1.3), reporting of adverse events (Section 8.3), and request to discontinue/withdraw from the study (Section 7.2) must be completed by the study participant; it is not permitted in Germany for these activities to be conducted by the participant's parents, designee, caregiver, surrogate, or legally authorized representative.

10.7. Appendix 7: Protocol JPCW Inducers and Strong Inhibitors of CYP3A

Strong Inducers of CYP3A
Aminoglutethimide
Apalutamide
Carbamazepine
Enzalutamide
Fosphenytoin (see also phenytoin)
Ivosidenib
Lumacaftor
Mitotane
Phenobarbital/phenobarbitone
Phenytoin
Rifabutin
Rifampicin (rifampin)
Rifapentine
St John's wort

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

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

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

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

Implementation of This Appendix

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

Exceptional Circumstances

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

Implementing Changes Under Exceptional Circumstances

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

Ethical review boards, regulatory bodies, and any other relevant local authorities, as required, will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation. If approval of ERBs, regulatory bodies, or both is required per local regulations, confirmation of this approval will be retained in the study records.

In the event written approval is granted by the sponsor for changes in study conduct, additional written guidance, if needed, will be provided by the sponsor.

Considerations for Making a Change

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

Informed Consent

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

- participation in remote visits, as defined in Section "Remote visits,"
- dispensation of additional study intervention during an extended treatment period,
- 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.

1. Remote visits

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.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.
Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures on the SoA may be performed at such visits.
Other alternative locations: Other procedures may be done at an alternate location in exceptional circumstances.

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

2. Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing with sponsor approval. However, central laboratory testing must be retained whenever possible for all visits where central laboratory testing is required. The local laboratory must be qualified in accordance with applicable local regulations.

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

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

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies

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.

4. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit(s) are valid for a maximum of 28 days as outlined in the study protocol. Informed consent can be signed up to 90 days prior to randomization; however, screening activities must be completed within 28 days prior to randomization. This screening period can be extended to 42 days under exceptional circumstances only. The following rules will be applied for active, nonrandomized participants who have signed informed consent and are undergoing screening procedures but whose participation in the study must be paused due to exceptional circumstances:

- If the screening period lasts for more than 42 days due to exceptional circumstances: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at screening visit(s) to ensure participant eligibility by Cycle 1 Day 1.

As of amendment (d), no new patients will be screened for study enrollment.

5. Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should follow the visit windows described in the SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance and approval 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.

As of amendment (d), the frequency of visits is at the discretion of the investigator. See the Continued Access SoA (See Section 1.3.1)

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visit 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 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.

10.9. Appendix 9: Abbreviations

Term	Definition
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BID	twice a day, at least approximately 6 hours apart
blinding	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BUN	blood urea nitrogen
CEC	Clinical Events Committee
CDK4 and 6	cyclin-dependent kinases 4 and 6
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIS	carcinoma in situ
CK	creatinine kinase
C_{max}	maximum serum/plasma concentration
C_{min}	minimum serum/plasma concentration
CMV	cytomegalovirus
CNS	central nervous system

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
CRP/CRS	Clinical Research Physician or Clinical Research Scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, CRS, global safety physician or other medical officer.
CT	computed tomography
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D. Bil	direct bilirubin
DCIS	ductal carcinoma in situ
DFS	disease-free survival
DMC	data monitoring committee
DNA	deoxyribose nucleic acid
DRFS	distant relapse-free survival
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
ECG	electrocardiogram
eBC	early breast cancer
eCOA	electronic Clinical Outcome Assessment
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.
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire Core 30
EQ-5D 5L	EuroQOL 5 Dimension 5 Level
ER	estrogen receptor

ERB	ethical review board
ERCP	endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
ET	endocrine therapy
F	frequency
FACT-GP5	Functional Assessment of Cancer Therapy-General item
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyltransferase
GnRH	gonadotropin-releasing hormone
HCRU	Health Care Resource Utilization
HDV	hepatitis D virus
HER2	human epidermal growth factor receptor-2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hormone receptor
HRQoL	health-related quality of life
I	interference
IB	Investigator's Brochure
IBTR	ipsilateral breast tumor recurrence
ICF	informed consent form
ICH	International Council for Harmonisation
iDFS	the absolute invasive disease-free survival
IDFS	invasive disease-free survival
IEC	independent ethics committees

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 boards
IRC	Internal Review Committee
ITT	intent-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.
IUD	intrauterine device
IV	intravenous
IWRS	interactive web-response system
LCIS	lobular carcinoma in situ
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
OS	overall survival
PA	posteroanterior
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
pCR	pathological complete response
PE	pulmonary embolism

PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetics
PO	by mouth
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT	prothrombin time
QTc	corrected QT interval
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
S	severity
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SMD	senior management designee
SoA	Schedule of Activities
TBL	total bilirubin
T-DM1	trastuzumab emtansine
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.
TKI	tyrosine kinase inhibitor
TTR	time to response
ULN	upper limit of normal
UK	United Kingdom
US	United States
VAS	visual analog scale

VTE	venous thromboembolic event
WOCBP	Women of childbearing potential

10.10. Appendix 10: Protocol Amendment History

Amendment [c]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to make the changes noted in the below bullets and as summarized in the table. Minor editorial changes are not included in the table.

- Modified definition of high risk in those treated with neoadjuvant therapy to include at least 1 lymph node, or residual disease of ≥5 cm, or a residual tumor of any size that has direct extension to the chest wall and/or skin (ulceration or skin nodules).
- For those treated with neoadjuvant chemotherapy, removed the requirement that TDM1 be the first therapy in the adjuvant setting.
- Extended the allowed time from definitive surgical resection to randomization to 20 months

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Modified definition of high risk in participants who received neoadjuvant therapy and participants who had definitive surgery prior to systemic therapy	For clarity
1.3 Schedule of Activities (section text)	Updated the language describing when participants have in-clinic visits and telephone visits	For clarity
	Added Summary of Visit Type by Cycle table	

1.3 Schedule of Activities (table)	Hematology row: Updated last bullet point to "Sample must be taken either within 14 days of C1D1 or on C1D1."	For clarity
	Bilateral imaging row: Added bullet point "Ultrasound alone is not sufficient for bilateral imaging."	
	Participant PRO daily e-diary row: Updated first bullet point to "Screening: collect at least 1 day and up to 7 days of daily data in the week prior to starting blinded study drug on C1D1."	
	HCRU row: Added a cross-reference to Section 8.10.3	
1.3.1. Pharmacokinetics, Genetics, and Biomarker Sampling Schedule	In Sampling Schedule for Genetics/Biomarkers table, added "if available" to comment for required archival tumor tissue (biomarker) row	For clarity
2.1 Study Rationale	Modified definition of high risk in participants who received neoadjuvant therapy and participants who had definitive surgery prior to systemic therapy	For clarity
2.2 Background	Added justification for changes to high-risk definition for those treated with neoadjuvant therapy	For clarity
5.1 Inclusion Criteria	Inclusion Criterion 2: Removed "in initial diagnostic tissue"	For clarity
	Inclusion Criterion 3: Revised descriptions of definitive surgery of the primary breast tumor(s)	
	Inclusion Criterion 4: Revised definitions of high-risk disease criteria and note regarding tumor size. Added notes regarding lymph node involvement and histology grade	
	Inclusion Criterion 5: Updated 18 months to 20 months	To accommodate real-world practice

	Inclusion Criterion 6: Revised duration of HER2-targeted therapy and eligible adjuvant HER2-targeted regimens	For clarity
	Inclusion Criterion 15b1: Revised guidance for abstinence and refraining from sexual intercourse with males during study intervention period	
5.2 Exclusion Criteria	Exclusion Criterion 17: Removed "Lymph node negative status". Added "Participants are required to have residual primary tumor and/or lymph node disease at the time of definitive surgery as indicated in inclusion criteria."	For clarity
	Exclusion Criterion 22: Added "This includes a history of catheter-associated thromboses."	
	Exclusion Criterion 25: Added "T-DXd" along with DS8201	For additional detail
	Exclusion Criterion 27: Removed "therapy for their breast cancer"	For clarity
6.1 Study Intervention(s) Administered	Abemaciclib/Placebo: Removed "open" from last sentence	For clarity; this is a reference to capsules instead of tablets
6.4 Study Intervention Compliance	Added compliance guidance and paper dosing diary instructions	For clarity
6.5.1 Supportive Care	Clarified reasons for early discontinuation from study treatment	For clarity
6.5.2 Supportive Management for Diarrhea in Participants Receiving Blinded Study Intervention	Added "at the initiation of study treatment" timing to when participants should receive instructions on the management of diarrhea	For clarity
6.6.1 Dose Suspension and Cycle Delay	Added instructions for dose adjustment based on lab results	For clarity
	Revised section to clarify that Day 1 of a cycle is when study drug is dispensed or contact is made with a patient for a phone visit	

7.1 Discontinuation of Study Intervention	Added a new bullet point to this list from Section 7.2: "Enrollment in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study	For clarity
7.1.1 QTc Stopping Criteria	Removed this section	This information is not needed
7.2 Participant Discontinuation/Withdrawal from the Study	Removed bullet points that are already included in Section 7.1 Updated reference to Visit 801 to clarify that a short-term follow-up visit (V801) should be conducted at the time of discontinuation	For clarity
8.2.1 Clinical Safety Laboratory Assessments	Updated CRF guidance: "Additionally, if local laboratory results are used to make a treatment decision, the results must be entered into the CRF."	For clarity
8.10.2 Electronic Participant Daily e-Diary Assessment	Updated collection instructional text for clarity. Added "can include C1D1 if prior to starting blinded study drug" to screening period guidance	For clarity
	Updated instructions for the eight items collected. Removed "in the order below"	
10.2 Appendix 2: Clinical Laboratory Tests	Updated guidance about discrepancies between local and central laboratory results	For clarity
	Updated "Neutrophils, segmented" to "Neutrophils, absolute". Removed "Monocytes," "Eosinophils," "Basophils," and "Erythrocytes (RBC)"	
	Updated pregnancy test information to include "A serum pregnancy test is required at screening."	

10.9 Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances	Updated Screening period guidance	For clarity
10.11 Appendix 11: Protocol Amendment History	Added amendment history from Study JPCW(b)	Current protocol version is Study JPCW(c)

Amendment [b]

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

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 rationale for this amendment is to make the changes noted in the below bullets and as summarized in the table. Minor editorial changes are not included in the table.

- Modified definition of high risk with regard to histologic grade, restricting it to participants with histologic Grade 3 disease.
- Resolved conflict between Inclusion Criteria 8 and 13; participants will not have to discontinue standard of care endocrine therapy received during the adjuvant anti-HER2 therapy for early breast cancer.
- Provided a conditional clause regarding the timing of the planned interim analysis in Section 9.4.2 (Primary Endpoint[s]).

Section	Description of Change	Brief Rationale
1.1 Synopsis	Changes in word choice when describing HR+, HER2+ breast cancer risk and risk of recurrence.	For clarity
1.1 Synopsis	Added citations for risk of disease recurrence.	For clarity
1.1 Synopsis	In defining "high risk" for eMonarcHER, revised wording to "participants who undergo surgery prior to administration of systemic therapy must have the following high-risk features and have completed adjuvant treatment with chemotherapy and HER2-targeted therapies (trastuzumab and pertuzumab):…."	For clarity
1.1 Synopsis	In defining "high risk" for eMonarcHER, histological Grade 2 was deleted, leaving just Grade 3.	To address FDA request.
1.2 Schema	Added heading boxes to the study schema to better label Study Intervention and Follow-up periods.	For clarity
1.3 Schedule of Activities (section text)	Updated the language describing when participants have in-clinic visits – accounting for the new Cycle 4 in-clinic visit.	Cycle 4 will now have an in-clinic visit.
1.3 Schedule of Activities (section text)	Minor edits in word choice.	For clarity
1.3 Schedule of Activities (table)	Edited header label for Cycles 14-24 to "Cycles 13-26" and incorporated column Cycle 26 D1.	For efficiency and clarity
1.3 Schedule of Activities (table)	Removed tolerance days for Cycle 1 Day 1, and added footnote defining C1D1 as date of first dose of blinded study drug.	For clarity regarding C1D1

1.3 Schedule of Activities (table)	In the header instructions, added Cycle 4 as a Clinic visit and removed Cycle 4 from Phone visits.	Added Cycle 4 as clinic visit in order to accommodate hematology and hepatic testing in Cycle 4.
1.3 Schedule of Activities (table)	ECOG PS: Updated instructions: assess at C1, C2, and all subsequent in-clinic visits; and added V801.	For clarity
1.3 Schedule of Activities (table)	ECG: Moved the "X" to just the "≤28 days" column.	For clarity
1.3 Schedule of Activities (table)	Hematology and Clinical Chemistry line items: Added a bullet point "If collected at baseline (≤14d from C1D1), then may be used in place of a C1D1 collection".	Allow sample collected at baseline to be used in place of C1D1 collection.
1.3 Schedule of Activities (table)	Hematology and Clinical Chemistry line items: Removed "X" from Long-term follow-up.	Sample is not necessary during long-term follow-up.
1.3 Schedule of Activities (table)	Pregnancy test: Added occurrence "X" to C1D1.	For clarity on C1D1.
1.3 Schedule of Activities (table)	Participant PRO questionnaire: Updated line-item title and clarified instructions related to administration method and occurrence. Removed "X" from Long-term follow-up.	For clarity
1.3 Schedule of Activities (table)	Participant PRO daily e-diary: Updated collection instructions.	For clarity
1.3 Schedule of Activities (table)	Participant Paper Diary: Updated instructions to remind sites to distribute diary on C1D1.	For clarity
1.3 Schedule of Activities (table)	Survival assessment: removed instructions.	Instructions are not necessary.
1.3 Schedule of Activities (table)	Administer abemaciclib/placebo: Deleted "See instructions" from C1D1 cell. This row was also shifted up in the SoA, above "Sample collection" procedure subheading.	For clarity - Perform as indicated by "X" spanning on-study period.
1.3 Schedule of Activities (table)	Administer ET: This row was shifted up in the SoA, above "Sample collection" procedure subheading.	For clarity
1.3 Schedule of Activities (table)	Abemaciclib/placebo drug accountability: Added line item.	For clarity – as reminder
1.3 Schedule of Activities (table)	ET Compliance: Added line item.	For clarity – as reminder
1.3 Schedule of Activities (table)	PK: Sampling schedule instructions updated.	For clarity
1.3 Schedule of Activities (table)	Whole blood for genetic/biomarker analysis: Updated line-item title and instructions.	For clarity

1.3 Schedule of Activities (table)	Serum for biomarkers: Added this line item.	New procedure item added for collecting serum sample for biomarkers.
1.3 Schedule of Activities (table)	Tumor tissue for biomarkers: Moved the "X" to just the "≤28 days" column.	For clarity
1.3 Schedule of Activities (table)	Updated footnote "c" with specific frequency and duration.	For clarity – as reminder
1.3.1 Pharmacokinetic, Genetics, and Biomarker Sampling Schedule (text)	For subsection, Sampling Schedule for Pharmacokinetics, updated the section methods content – making it more explicit.	For clarity
1.3.1 Pharmacokinetic, Genetics, and Biomarker Sampling Schedule	PK Sampling Schedule table: Added superscript "f" to "2-8 hours" of Cycle 1 Day 1 Sample Number 1, Cycle 2 Day 1 Sample Number 2, and Cycle 3 Day 1, Sample Number 5.	Error correction
1.3.1 Pharmacokinetic, Genetics, and Biomarker Sampling Schedule	Sampling Schedule for Genetics/Biomarkers: Added line item for collection of Serum (biomarker).	To align with needs in Genetics/Biomarker sections.
2.1 Study Rationale	Added citations Lambertini et al. 2019 and Ortega et al. 2002.	To support grade as factor in risk of recurrence (Lambertini et al. 2019); and D-type cyclins in cell growth (Ortega et al. 2002).
2.1 Study Rationale	Updated text related to approved indications for abemaciclib.	For clarity
2.1 Study Rationale	Updated definition of high risk used for entry to monarchE.	For clarity
2.1 Study Rationale	In defining "high risk" for eMonarcHER, revised wording to "participants who undergo surgery prior to administration of systemic therapy must have the following high-risk features and have completed adjuvant treatment with chemotherapy and HER2-targeted therapies (trastuzumab and pertuzumab):…."	For clarity
2.1 Study Rationale	For eMonarcHER, the definition of high risk was updated to delete histological Grade 2.	Per FDA request.
2.2 Background	Added citation for von Minckwitz et al. 2019.	Support of residual disease as a risk feature for distant relapse.
2.2.6 Abemaciclib	Deleted redundant block of background text regarding mechanism of action of abemaciclib.	For clarity
2.2.6 Abemaciclib	Updated definition of high risk used for entry to monarchE.	For clarity

2.3.1 Risk Assessment	Grade ≥3 Diarrhea: In summary of data, added specific study names for clarity, and added data for monarchE. In mitigation strategy, deleted monitoring of renal function and vital signs.	For clarity and completeness
2.3.1 Risk Assessment	Grade ≥3 Neutropenia: In summary of data, added specific study names for clarity, made correction for Grade ≥3 neutropenia in Monarch 3 (21%) and Monarch 2 (27%), and added data for monarchE. In mitigation strategy, updated the lab monitoring timing.	For clarity, accuracy, and completeness. Addition of laboratory monitoring in Cycle 4.
2.3.1 Risk Assessment	Interstitial Lung Disease (ILD)/Pneumonitis: In summary of data, added data for monarchE, and deleted "potentially limited tolerability".	For completeness and clarity
2.3.1 Risk Assessment	Grade ≥3 ALT increased: In summary of data, added specific study names for clarity, made a correction (4% to 6%), and added data for monarchE. Clarified text in ALT elevations section. In median time to onset section, clarified text and made correction (Monarch 3: 61 days). In mitigation strategy, updated the lab monitoring timing.	For clarity, completeness, and accuracy. Addition of laboratory monitoring in Cycle 4.
2.3.1 Risk Assessment	Venous Thromboembolic Events (VTE): In summary of data, added specific study names for clarity, and added data for monarchE.	For clarity and completeness
4.3 Justification for Dose	Minor formatting change, and added "Therefore, standard adjuvant ET will be administered per label or local guidelines at the recommended dose."	For clarity
5.1 Inclusion Criteria	Inclusion Criterion 2c: Refined eligibility criteria related to disease characteristics.	For consistency with standard of care and real-world practice.
5.1 Inclusion Criteria	Inclusion Criterion 4a: Replaced "trastuzumab-based" with "HER2-targeted" and deleted "trastuzumab monotherapy or in combination with other HER2-targeted therapies".	For clarity
5.1 Inclusion Criteria	Inclusion Criterion 4bii1: Deleted histologic Grade 2 from the high-risk eligibility criteria. Remains at histologic Grade 3.	Per FDA request
5.1 Inclusion Criteria	Inclusion Criterion 8: Edited wording to remove apparent conflict with Inclusion Criterion 13.	Per FDA request, for clarity

5.1 Inclusion Criteria	Inclusion Criterion 13: Added wording to remove conflict with Inclusion Criterion 8.	Per FDA request. Restriction on the use exogenous reproductive hormone therapy does NOT apply to ET (tamoxifen or AI) being administered as part of adjuvant therapy for early breast cancer.
5.1 Inclusion Criteria	Inclusion Criterion 15b2: Modified text, adding "or serum" to urine, as type of pregnancy test type that can be used within 24 hours prior to exposure.	To allow flexibility at site
5.2 Exclusion Criteria	Exclusion Criterion 21: Deleted "active symptoms" related to ILD/pneumonitis.	For clarity
5.3 Lifestyle Considerations	Correction: replaced "chemotherapy" with "endocrine therapy".	Error correction
5.4 Screen Failures	Updated wording for interval between screen failure and rescreening.	For clarity
6.1 Study Intervention(s) Administered	Endocrine therapy: in the sentence, "A switch to another standard ET in allowed..." deleted "only in the absence of an IDFS event".	For clarity
6.4 Study Intervention Compliance	Modified wording to align with the new abemaciclib/placebo drug accountability, and ET Schedule of Activities, rows in the Schedule of Activities.	For clarity
6.5 Concomitant Therapy	Clarified that concomitant medications should be recorded through the on-study intervention period and short-term follow-up period.	For clarity
6.6.1 Dose Suspension and Cycle Delay	Revised section to clarify text for dose suspensions before and after minor and major surgical procedures.	For clarity
7.1 Discontinuation of Study Intervention	Modified discontinuation of study intervention text to reduce redundancy. Added cross reference to Section 1.3 (Schedule of Activities) to add clarity regarding procedures to be performed upon discontinuation from study intervention. Removed paragraph ("In rare instances..") to reduce redundancy. Moved QTc paragraph down to new Section 7.1.1 to improve flow and clarity. Deleted sentence "After discontinuation are met…" due to redundancy with prior content in the section.	Removed redundant text for improved flow and clarity.
7.1.1 QTc Stopping Criteria	Moved QTc text block from Section 7.1 to new subsection 7.1.1.	For improved flow

7.2 Participant Discontinuation/Withdrawal from the Study	Added reference to Visit 801 to clarify data to be collected at the time of discontinuation and follow-up.	For clarity
8.2 Safety Assessments	Deleted "and functional" from the text describing monitoring for testicular changes.	To clarify what we are expecting to be monitored.
8.2.3 Venous Thromboembolic Events (VTEs)	Replaced study codes with study names.	For clarity
8.2.3 Venous Thromboembolic Events (VTEs)	Updated with sentence - "The majority of patients who experienced VTEs were treated with anticoagulants."	For clarity
8.2.3 Venous Thromboembolic Events (VTEs)	Deleted block of text pertaining to adjudication of VTEs.	Based on experience with monarchE, adjudication of non-confirmed cases of VTE is no longer required since only a low number of events were adjudicated and it had no impact in the overall frequency of VTE identified.
8.2.5 Interstitial Lung Disease (ILD)/Pneumonitis	Remove block text citing ILD/pneumonitis safety data in MONARCH 1, MONARCH 2, and MONARCH 3.	These data are redundant with data presented in Section 2.3.1.
8.5 Pharmacokinetics	Minor edits for clarity related to sample collection.	For clarity
8.7 Genetics	All section content updated.	Updated to clarify intended genetic research in this study.
8.8 Biomarkers	All section content updated.	Updated to clarify intended biomarker research in this study.
8.10.1 Patient-Reported Outcomes (PRO)	Updated opening sentence to clarify that PROs will be collected in the order listed, and prior to extensive contact with site personnel.	For clarity
8.10.2 Electronic Participant Daily e-Diary Assessment	Updated collection instructional text for clarity.	For clarity
9.4.2 Primary Endpoint(s)	Provided a conditional clause regarding the timing of the planned interim analysis.	Change was made to address FDA request. Clarified timing and strategy of planned interim efficacy analysis relative to final IDFS analysis.
9.4.6.4 Treatment Compliance	Aligned text related to ET compliance with SoA.	For clarity
10.2 Appendix 2: Clinical Laboratory Tests	Added text to state that discrepancies between local and central laboratory results will not be considered protocol deviations.	For clarity
10.2 Appendix 2: Clinical Laboratory Tests	Added cross-reference to Section 8.2.2.(Hepatic Safety Monitoring) and Appendix 5 (Liver Safety).	For clarity and ease of use

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Updated definition of females considered not of child bearing potential.	To align definition in appendix with definition in Inclusion Criterion 15b3.
10.6.2 Appendix 6: Removal of the Legally Authorized Representative, Legal Guardian, Parents, Designee, Surrogate, and Caregiver in Germany	Added text for Germany, requiring the participant to complete the ICF, AE, and discontinuation/withdrawal processes, and not a legally authorized representative, legal guardian, parent, designee, surrogate, or caregiver.	Per request of German Ethics Committee.
10.7 Appendix 7: Protocol JPCW Inducers and Strong Inhibitors of CYP3A	Updated list of inducers and strong inhibitors.	To provide the current list of inducers and strong inhibitors.
10.8 Appendix 8: Protocol JPCW Breast Cancer Recurrence and Other Cancer Events	Edited bullet 2 to clarify breast cancer recurrence language.	For clarity
10.11 Protocol Amendment History	Added amendment history from Study JPCW(a).	Current protocol version is Study JPCW(b).

Abbreviations: ALT = alanine aminotransferase; C1 = Cycle 1; d = day; D1 = Day 1: ET = endocrine therapy; FDA = Food and Drug Administration; HR+ = hormone receptor-positive; HER2+ = human epidermal growth factor receptor-2 positive; IDFS = invasive disease-free survival; ILD = interstitial lung disease; PK = pharmacokinetic; PRO = patient-reported outcomes; QTc = QT interval corrected; V801 = visit 801; VTE = venous thromboembolic event.

Amendment [a]

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:

Based on the grounds for non-acceptance (GNAs) resulting from the voluntary harmonization procedure (VHP) assessment and additional Lilly items, this amendment addresses

- minor edit in Schema
- changes to the Schedule of Activities
- changes to the Inclusion and Exclusion Criteria
- correction in Risk Assessment table
- corrections to CYP3A guidance text
- text moved to Discontinuation of Study Intervention
- added text to Safety Assessments
- changes in futility interim analyses text
- removed select contraception text in Appendix 4
- other changes and clarifications throughout the protocol

Section	Description of Change	Brief Rationale
1.2 Schema	Edited study schema - Changed neoadjuvant "trastuzumab" in bottom row to "HER2 targeted therapy"	To clarify neoadjuvant
1.3 Schedule of Activities (text section)	Moved block of text related to V801 to the Short-term follow-up section directly below original location.	Moved for clarity
1.3 Schedule of Activities (text section)	Moved discontinuation text in Short-term follow-up to Section 7.1 (Discontinuation of Study Intervention).	Moved for clarity to Discontinuation section
1.3 Schedule of Activities (text section)	Minor edit in Long-term follow-up text – added the word "…including…" in the 2nd paragraph.	Added for clarity
1.3 Schedule of Activities (SoA)	Added a visit column for Cycle 26 Day 28 to improve clarity regarding which procedures to be completed.	Added as aid to investigators/sites
1.3 Schedule of Activities (SoA)	Added a footnote explaining the timing of Short-term follow-up.	Added for clarity
1.3 Schedule of Activities (SoA)	Added a footnote explaining the timing of Long-term follow-up.	Added for clarity

1.3 Schedule of Activities (SoA)	Refined Cycle and Day headings for clarity.	Added for clarity
1.3 Schedule of Activities (SoA)	Edited instructions for Clinic visits and Phone visits.	To clarify type of visits needed for each cycle during study
1.3 Schedule of Activities (SoA)	Edited procedure for Pregnancy test, removing required test at V801, and editing instructions for clarity.	Clarity for procedure frequency and timing
1.3 Schedule of Activities (SoA)	Abdominal ± pelvic imaging – edited formatting - referred to instructions. Added clarifying text in instructions for During treatment "and follow-up.."	Clarity for procedure
1.3 Schedule of Activities (SoA)	For Bilateral imaging - in Short-term follow-up (V801), removed "X" – edited formatting - referred to instructions. Added clarifying text in instructions for During treatment "and follow-up.."	Clarity for procedure
1.3 Schedule of Activities (SoA)	Chest imaging – edited formatting - referred to instructions. Added language to clarify that imaging must be performed prior to randomization. Added clarifying text in instructions for During treatment "and follow-up.."	Clarity for procedure
1.3 Schedule of Activities (SoA)	Bone nuclear imaging – edited formatting - referred to instructions. Added clarifying text in instructions for During treatment "and follow-up.."	Clarity for procedure
1.3 Schedule of Activities (SoA)	Added procedure row for Participant Paper Diary for tracking date/time of abemaciclib/placebo doses taken.	As aid for investigators and sites
1.3 Schedule of Activities (SoA)	Minor add - note to PK procedure row cross-referencing to paper diary.	As aid for investigators and sites
1.3 Schedule of Activities (SoA)	For Plasma for biomarker item, clarified instructional note for consistency with biomarker sampling schedule in Section 1.3.1.	Clarity for procedure
2.3.1 Risk Assessment	Corrected text in first column, first row to Grade ≥3 Diarrhea.	Correction GNA 8
5.1 Inclusion Criteria	Inclusion Criterion 2: Added STEEP criteria in text and cross reference to Appendix 8.	GNA 1 Added for clarity
5.1 Inclusion Criteria	Inclusion Criterion 4: added parenthetical explanation to "trastuzumab-based therapy" - (trastuzumab monotherapy or in combination with other HER2-targeted therapies).	Added for clarity
5.1 Inclusion Criteria	Inclusion Criterion 6: Edited language for required duration (approximately 9 months to 1 year) of standard HER2-targeted therapy.	GNA 2 Added for clarity
5.1 Inclusion Criteria	Inclusion Criterion 6a and 6b: Added clarifying language for eligible adjuvant regimens.	GNA 2 Added for clarity

5.1 Inclusion Criteria	Inclusion Criterion 15: Modified IC 15a for male participants, replaced "during the intervention period" with "while taking blinded study drug"; and added "The use of contraception in male participants is not required." Modified IC 15b-2 for female participants, to add 3 weeks to time requirement for using highly effective contraception following last dose of blinded study drug. Also deleted subpoints B and C.	GNA 10 Updated to align with current guidance
5.2 Exclusion Criteria	Exclusion Criterion 23: Added word "known".	GNA 3 Added for clarity
5.2 Exclusion Criteria	Exclusion Criterion 23a: Added units "µL" to cell count (cells/µL).	Correction
5.2 Exclusion Criteria	Exclusion Criterion 28: Deleted.	Medical decision
6.5 Concomitant Therapy	Added sentence stating that concurrent treatment with standard of care bone-modifying agents is permitted.	Added for clarity
6.5 Concomitant Therapy	Replaced "abemaciclib" with "blinded study drug".	GNA 12 Correction
6.5 Concomitant Therapy	Transporter Substrates section: Added descriptive text "At clinically relevant concentrations…" at start of section text.	Added for clarity
7.1 Discontinuation of Study Intervention	Inserted discontinuation explanatory text that was moved from Section 1.3.	Added for clarity
8.1.1 Imaging and Recurrence Assessment	Changed section title to better reflect content.	Changed for clarity
8.2 Safety Assessments	Added content addressing monitoring participants for signs and symptoms of visual impairment and/or testicular anatomical and functional changes.	GNA 9 Added for clarity
8.5 Pharmacokinetics	Inserted minor text and corrected visit text for PK sampling.	Correction
9.5.1 Interim Analyses for Efficacy/Futility	Added content further detailing the process of the futility interim analyses.	GNA 16 Added for clarity
10.2 Appendix 2	Labs test removed for Cell morphology (RBC and WBC).	This lab test is not necessary
10.4 Appendix 4	Contraception Guidance: CONTRACEPTIVES ALLOWED DURING THE STUDY. Removed block of text: "If the highly effective contraceptive methods are contraindicated or strictly declined by the patient… …or sponge with spermicide (double-barrier method) is also considered an acceptable birth control method."	Updated to align with current guidance
10.8 Appendix 8	Minor modification of text related to the definition of Distant Recurrence for clarity.	Added clarity

Throughout Document	Minor editorial and format changes.	Editorial

Abbreviations: HER2 = human epidermal growth factor receptor-2; PK = pharmacokinetics; RBC = red blood cell; STEEP = Standardized Definitions for Efficacy Endpoints; V = visit; WBC = white blood cell.

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