Protocol Amendment J2J-MC-JZLB (b)

EMBER-2: A Phase 1, Open-Label, Preoperative Window Study evaluating the Biological Effects of LY3484356 in Post-menopausal Women with Stage I-III Estrogen Receptor-Positive, HER2-Negative Breast Cancer

NCT04647487

Approval Date: 18-Jan-2022

Title Page

Protocol Title: EMBER-2: A Phase 1, Open-Label, Preoperative Window Study evaluating the Biological Effects of LY3484356 in Post-menopausal Women with Stage I-III Estrogen Receptor-Positive, HER2-Negative Breast Cancer

Protocol Number: J2J-MC-JZLB

Compound: LY3484356 (imlunestrant)

Amendment: (b)

Study Phase: Phase 1

Short Title: EMBER-2: A Preoperative Window Study of LY3484356 in Stage I-III Estrogen Receptor-Positive Breast Cancer

Acronym: JZLB

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 145311

EudraCT: 2020-002810-42

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

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment a	10-Dec-2020
Protocol J2J-MC-JZLB	31-Aug-2020

Amendment (b)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This amendment incorporates an additional dose level (200mg) cohort, at the dose level below the recommended Phase 2 dose (RP2D) of LY3484356.

The RP2D of LY3484356 was determined as 400 mg in the EMBER study, a Phase 1a/1b dose escalation and dose expansion study of LY3484356 in advanced breast and endometrial cancer participants. Occasionally, dose reduction of LY3484356 to 200 mg is necessary due to AEs observed at the RP2D (400 mg).

Therefore, in this study amendment (b), we aim to determine the biologic effects of this lower dose level (200 mg) through evaluation of changes in ER (primary objective), PR and Ki67 (secondary objectives) expression at the 200 mg dose.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.2 Schema; 2.1 Study Rationale; 4.1 Overall Design; 4.3 Justification for Dose; 6.1 Study Intervention(s) Administered	Addition of Cohort C to study design	Added cohort to evaluate ER, PR, and Ki67 change in expression at 200 mg dose level
1.3 Schedule of Activities	Added Visit 1 window to vital signs, hematology, clinical chemistry, whole blood (PGx)	Added for flexibility
1.3 Schedule of Activities	Moved window for biomarker plasma to Day 1	Operational
1.3 Schedule of Activities	Added concomitant medication collection to short-term follow-up visit	Operational
2.2 Study Background	Updated background to incorporate new information	Updated to include most recent information on LY3484356 from EMBER and EMBER-2 trials
2.3 Benefit/Risk Assessment	Updated section with most recent safety information on LY3484356	Emerging safety information
5.2 Exclusion Criteria	Added Exclusion #28	Criterion was erroneously omitted
6.3 Measures to Minimize Bias: Randomization and Blinding	Added description for the 200 mg cohort (Cohort C)	Updated to reflect changes to study design

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy; 10.7 Appendix 7: Other CYP-sensitive Substrates; 10.8 Appendix 8: Examples of strong clinical inhibitors and inducers of UGT1A1	Updated concomitant therapy guidance; updated appendices, removed appendix of P-gp inhibitors	Alignment with current guidance for LY3484356
9.2 Sample Size Determination; 1.1 Synopsis	Updated total sample size	Updated to reflect changes to study design
10.2 Appendix 2: Clinical Laboratory Tests	Clarified reporting of abnormal values; specified discrepancies between local and central laboratory results will not be considered protocol deviations	Clarification
10.9 Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added appendix	Added to provide flexibility for study participants during exceptional circumstances
Throughout the protocol	Minor editorial and formatting changes	Minor; therefore, not detailed

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1. Protocol Summary

1.1. Synopsis

Protocol Title: EMBER-2: A Phase 1, Open-Label, Preoperative Window Study evaluating the Biological Effects of LY3484356 in Post-menopausal Women with Stage I-III Estrogen Receptor-Positive, human epidermal growth factor receptor 2 negative (HER2-) Breast Cancer

Short Title: EMBER-2: A Preoperative Window Study of LY3484356 in Stage I-III Estrogen Receptor-Positive Breast Cancer

Rationale:

Study J2J-MC-JZLB (JZLB) is designed to assess pharmacodynamics (PD), pharmacokinetic (PK), and biologic effects and safety of the selective estrogen receptor degrader (SERD), LY3484356, in patients with estrogen receptor-positive (ER+), HER2- early stage (Stage I to Stage III) breast cancer, in order to compare the biologic activity of different doses of the drug. Patients will be randomized to one of multiple dose levels of LY3484356 with study objectives compared across each treatment arm.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Determine PD effect of each dose level of LY3484356 on ER expression, in patients with ER+ early stage breast cancer.	• Change in ER expression (as measured by IHC and quantified by H-score) between pre- and on-treatment tumor samples, at each dose level of LY3484356
Secondary	
• Assess PD effect of each dose level of LY3484356 on Tumor cell proliferation.	• Change in Ki-67 (as measured by IHC and expressed by % positive scoring) between pre- and on-treatment tumor samples, at each dose level of LY3484356
• Assess PD effect of each dose level of LY3484356 on PR expression.	• Change in PR expression (as measured by IHC and quantified by H score) between pre- and on-treatment tumor samples, at each dose level of LY3484356
• Evaluate safety and tolerability of each dose level of LY3484356.	• Incidence of investigator assessed AEs per NCI CTCAE v5.0, at each dose level of LY3484356
• Evaluate PK effect of each dose level of LY3484356.	• Plasma concentrations of LY3484356, at each dose level of LY3484356

Exploratory	
CCI	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ER = estrogen receptor; IHC = immunohistochemistry; NCI = National Cancer Institute; PD = pharmacodynamics; PK = pharmacokinetics; PR = progesterone receptor.

Overall Design: Study JZLB is a Phase 1 open-label, randomized pre-operative window study of LY3484356 in post-menopausal women with Stage I to Stage III ER+, HER2- breast cancer who are scheduled for surgery with curative intent. Patients will consent to provide tumor samples obtained at the time of diagnosis and at the time of scheduled surgery or repeat biopsy, for the purpose of biomarker analyses. Patients will then be randomized to either 400 or 800 mg LY3484356 or directly assigned to the 200 mg dose and receive treatment for approximately 15 days, up to and including the day of scheduled surgery or repeat biopsy (if neoadjuvant therapy is subsequently planned). Tumor samples taken pre- and on-treatment with LY3484356, at the time of diagnosis and scheduled surgery/repeat biopsy, respectively, will then be evaluated for biologic effects, as outlined in the study objectives.

Disclosure Statement: This is a biomarker study in patients with early stage ER+ breast cancer with multiple treatment arms of LY3484356.

Number of Participants:

Approximately 90 participants with early stage ER+ breast cancer will be enrolled in this study. Patients will be randomized to either 400 or 800 mg LY3484356 or directly assigned to the 200 mg dose, with approximately 30 patients assigned to each dose level cohort.

Intervention Groups and Duration:

Patients enrolled in this Phase 1 open-label, preoperative study will receive 200 mg, 400 mg or 800 mg of LY3484356 as shown in the table below. Patients will start LY3484356 on Day 1 and continue it daily, up to and including the day of surgery or repeat biopsy on Day 15 (with an allowable window of -2 to +7 days). This pre-surgery/biopsy dose of LY3484356 will be the last dose of LY3484356 treatment on this study.

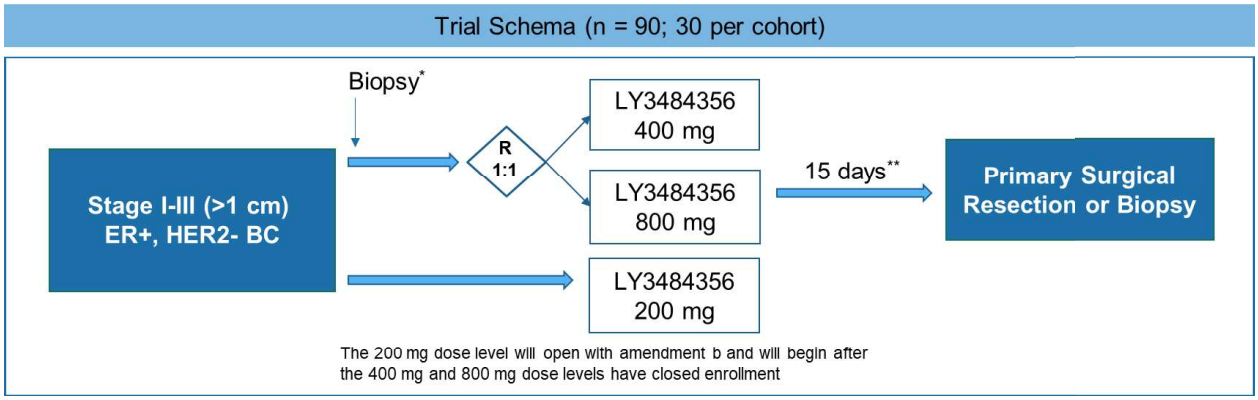
Study Drug	Cohort	Proposed Doses	Dose Schedule, Route of Administration, Duration
LY3484356	A	400 mg	QD, PO, administered for 15 days[a]
LY3484356	B	800 mg	QD, PO, administered for 15 days[a]
LY3484356	C	200 mg	QD, PO, administered for 15 days[a]

Abbreviations: PO = orally; QD = once daily.

a Allowable window to facilitate scheduling of on-treatment surgery/biopsy: Day 15 (- 2 to + 7 days, [ie, a range of 13 to 22 days of LY3484356 treatment will be permissible]). Patients should continue to dose study drug continuously through the day of surgery/biopsy, with the last dose of LY3484356 administered on the morning of surgery/biopsy.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: BC = breast cancer; ER+ = estrogen receptor positive; HER2- = human epidermal growth factor receptor 2 negative; R = randomize.

* Baseline (pre-treatment) tumor tissue collection:

- Adequate archival tissue, as defined in Section 8.8, from diagnostic biopsy is acceptable if collected within 6 weeks prior to consent.
- Fresh biopsy:
  - Required if archival tissue is unavailable/exhausted or was collected >6 weeks prior to consent or while the patient was taking Hormone Replacement Therapy
  - Optional for the purpose of Oncotype DX testing

See Section 8.8 for specifics regarding both baseline (pretreatment) and Day 15 (on-treatment) breast tumor tissue collections.

** Allowable treatment window to facilitate scheduling of on-treatment surgery/biopsy: 15 days (- 2 to + 7 days [ie, a range of 13 to 22 days of LY3484356 treatment will be permissible.])

1.3. Schedule of Activities

Screening, On-Study, and Post-Treatment Schedule of Activities						
Screening			**On-Treatment** Duration ~15 days (-2 to +7 days)		**Post-Treatment**	
	(Day Relative to Day 1) **≤28**	**Start of Treatment** **Day 1**	**Pre-Surgery/Biopsy Visit[a]** **Within 7 days prior to Surgery/Biopsy**	**Surgery or Biopsy** **Day 15** (-2 to +7 days)	**Short-term follow-up[b]** **30 days post-surgery/biopsy** (±14 days)	
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**Instructions**
Procedure						
Informed consent	X					ICF must be signed before any protocol-specific procedures are performed
Inclusion/exclusion criteria	X					
Medical history and description of primary breast cancer	X					• Complete assessment of prior medical, surgical and social history (such as tobacco and alcohol use). • From pathology report, record primary diagnosis, tumor grade, and any additional biomarker testing including receptor status (ER/PR/HER2) and Ki-67 (if reported) from the invasive breast cancer.
Clinical Tumor Measurement	X					Record estimated size of tumor and clinical stage (per AJCC) from pre-operative imaging study (mammogram, MRI or equivalent).
Vital signs	X	X	X		X	Measure vital signs (temperature, blood pressure, pulse rate, and pulse oximetry) may be performed ≤3 days prior to V1. V1&V2 vital signs should be measured before first dose. At V1, vital signs measurement will be also collected 3-4 hours post-dose.

Screening, On-Study, and Post-Treatment Schedule of Activities						
Screening			**On-Treatment** Duration ~15 days (-2 to +7 days)		**Post-Treatment**	
	(Day Relative to Day 1) **≤28**	**Start of Treatment** **Day 1**	**Pre-Surgery/Biopsy Visit[a]** **Within 7 days prior to Surgery/Biopsy**	**Surgery or Biopsy** **Day 15** (-2 to +7 days)	**Short-term follow-up[b]** **30 days post-surgery/biopsy** (±14 days)	
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**Instructions**
ECOG performance status	X	X	X		X	During study treatment, perform during clinic visits
Physical examination	X	X			X	Collect height and weight at baseline; weight only thereafter
ECG	X	X	X			Single local ECG: V1&V2 ECG should be collected before first dose. At V1, an ECG will also be collected 3-4 hours post-dose. For all visit ECGs, participant should be recumbent or semi-recumbent for 5 to 10 minutes before collection and during study.
Hematology	X	X	X		X	See Appendix 2 (Section 10.2). May be performed ≤3 days prior to V1
Clinical chemistry	X	X	X		X	See Appendix 2 (Section 10.2). May be performed ≤3 days prior to V1
Pharmacokinetics		X	X			See Section 1.3.1 for time points.
Whole blood (PGx)		X				Collect on Day 1/V1 or may be performed ≤3 days prior to V1
Biomarker plasma		X (pre-dose)	X			Plasma to be collected on V1 pre-dose or may be performed ≤3 days prior to V1. The V2 plasma can be collected anytime during the clinic visit
Follicle Stimulating Hormone (FSH) & estradiol	X					Only for patients who are <60 years of age

Screening, On-Study, and Post-Treatment Schedule of Activities						
Screening			**On-Treatment** Duration ~15 days (-2 to +7 days)		**Post-Treatment**	
	(Day Relative to Day 1) ≤28	**Start of Treatment Day 1**	**Pre-Surgery/Biopsy Visit[a] Within 7 days prior to Surgery/Biopsy**	**Surgery or Biopsy Day 15** (-2 to +7 days)	**Short-term follow-up[b] 30 days post-surgery/biopsy** (±14 days)	
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**Instructions**
Hepatitis B and C	X					
Coagulation	X					See Appendix 2 (Section 10.2). Perform at baseline and as clinically indicated
Urinalysis	X		X			See Appendix 2 (Section 10.2). Perform as clinically indicated.

Screening, On-Study, and Post-Treatment Schedule of Activities						
Screening			**On-Treatment** Duration ~15 days (-2 to +7 days)		**Post-Treatment**	
	(Day Relative to Day 1) **≤28**	**Start of Treatment** **Day 1**	**Pre-Surgery/Biopsy Visit[a]** **Within 7 days prior to Surgery/Biopsy**	**Surgery or Biopsy** **Day 15** (-2 to +7 days)	**Short-term follow-up[b]** **30 days post-surgery/biopsy** (±14 days)	
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**Instructions**
Breast tumor tissue	X			X		At baseline (pre-treatment): • Adequate archival tissue, from the diagnostic biopsy is acceptable if collected within 6 weeks. • Fresh baseline biopsy: o Required: If archival tissue is unavailable/exhausted or was collected >6 weeks prior to consent or while the patient was taking Hormone Replacement Therapy o Optional: For the purpose of Oncotype DX testing See Section 8.8 for specifics regarding both baseline (pre-treatment) and Day 15 (on-treatment) breast tumor tissue collections.
Surgical Pathology Report					X	Record size of lesion (L×W×D), primary diagnosis, pathological stage, tumor grade, complete histologic description, and any additional biomarker testing including receptor status (ER/PR/HER2) and Ki-67 (if reported) from the invasive breast cancer.

Screening, On-Study, and Post-Treatment Schedule of Activities						
	Screening		**On-Treatment** Duration ~15 days (-2 to +7 days)		**Post-Treatment**	
	(Day Relative to Day 1) **≤28**	**Start of Treatment** **Day 1**	**Pre-Surgery/Biopsy Visit[a]** **Within 7 days prior to Surgery/Biopsy**	**Surgery or Biopsy** **Day 15** (-2 to +7 days)	**Short-term follow-up[b]** **30 days post-surgery/biopsy** (±14 days)	
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**Instructions**
						This is only required for patients who provide surgical resection for on-treatment tissue collection.
Administer LY3484356		See Instructions				Administer according to Section 6.1.
Patient diary		See Instructions				Provide patient diary Day 1. Completed daily by patient until day of surgery. Review at each study visit. Collection of diary and reconciliation of study drug can occur at V3 or V4.
Concomitant medication	X	See Instructions			X	• At baseline, record prior and concurrent medications. • Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.
AE collection		See Instructions			X	Collect continuously at every visit and throughout the study using CTCAE Version 5.0

Abbreviations: AE = adverse event; AJCC = American Joint Committee on Cancer; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; ICF = informed consent form; L×W×D = length times width times depth; PGx = pharmacogenomics; PK = pharmacokinetic; PR = progesterone receptor; V = visit.

[a] Pre-op (V2) study assessments must occur within 7 days of the scheduled surgical/biopsy date (V3). These assessments may be coordinated with routine preoperative assessments or may occur, if necessary, on the morning of surgery/biopsy (V3), provided all V2 assessments (including 3 to 4 hour post-dose PK draw) are performed and the results of the clinical investigations are reviewed prior to surgery/biopsy.

[b] Short-term follow- up visit must occur 30 days ±14 days after surgery/biopsy or after resolution of all treatment related adverse effects whichever comes later.

1.3.1. Sampling Schedule for Pharmacokinetics

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

Visit	Sample time Relative to Dose	LY3484356 PK Sampling
V1 & V2[a]	Predose[b]	Plasma PK Sample
	3 to 4 hours post-dose[b]	Plasma PK Sample
+/- V3	Post-dose	Tumor PK Sample[c]

Abbreviations: PK = pharmacokinetic; V = visit.

a Pre-op (V2) study assessments may occur, if necessary, on the morning of surgery/biopsy (V3).

b Pre-dose and 3 to 4 hours post-dose PK sampling to be drawn on the same day.

c Optional but strongly encouraged. See Section 8.8 for specifics regarding the V3 (on-treatment) tumor tissue collections.

2. Introduction

2.1. Study Rationale

Selective estrogen receptor degraders are one of the treatment options for ER+/human epidermal growth factor receptor 2 negative (HER2-) breast cancer patients. In a recent large retrospective clinicopathologic study, Li and colleagues reported that 70.4% of breast cancers are ER+ (Li et al. 2019). Fulvestrant is currently the only regulatory agency-approved SERD for the treatment of ER+ metastatic breast cancer (mBC) (Nardone et al. 2019; Soleja et a. 2019). Its efficacy is highly dose-dependent, where increasing the administered dose has led to improved survival (Robertson et al. 2004; Robertson and Harrison 2004; Di Leo et al. 2014). However, even though doses higher than 500 mg per month may lead to better ER degradation, the intramuscular (IM) administration route limits the amount of fulvestrant that can be given to patients (Nardone et al. 2019). In addition, several studies have shown that with the current maximum feasible dose, fulvestrant treatment is not able to completely degrade ER in patients and can be associated with early progression (van Kruchten et al. 2015). Thus, there is unmet medical need to develop oral SERDs with higher bioavailability, greater ER targeting, and degradation capabilities (Nardone et al. 2019).

Study J2J-MC-JZLB (JZLB) is a short-term, preoperative, randomized Phase 1 study comparing the biologic activity of different doses of the SERD, LY3484356. The purpose of this study is to assess PD, PK, and biologic effects and safety of LY3484356, in patients with ER+ early stage (Stage I to Stage III) breast cancer. Patients will be randomized to either 400 mg or 800 mg dose levels of LY3484356 with study objectives compared across the treatment arms. No randomization will occur for the 200 mg level as this dose level will open after the 400 and 800 mg dose levels are closed.

2.2. Study Background

Breast cancer is the most frequent cancer among women and is a major cause of cancer-related deaths worldwide. It is estimated that more than 2 million new cases of breast cancer occurred worldwide in women in 2018 (Bray et al. 2018). Clinical decision-making for the management of patients with breast cancer considers multiple clinical factors such as ER/HER2 status, age, comorbidities, and patient preference. More specifically, treatment options for women with breast cancer are largely determined by tumor ER and HER2 status (NCCN 2018; Waks and Winer 2019).

Over two-thirds of breast cancers express ER, which is a key driver of breast cancer initiation and progression. Endocrine therapies aim to reduce ER activity and include strategies such as direct ER modulation (tamoxifen), systemic prevention of the conversion of androgens to estrogens using aromatase inhibitors (AIs; letrozole, anastrozole, and exemestane), and SERDs (fulvestrant) that block and degrade the ER.

Currently, fulvestrant is the only regulatory agency-approved SERD (Soleja et al. 2019) for the treatment of ER+ mBC in patients who are endocrine therapy naïve or after progression on tamoxifen or aromatase inhibitors. However, it has several limitations. Due to its insoluble nature with poor oral bioavailability and a short intravenous half-life, fulvestrant needs to be given IM and is highly dose-dependent (Robertson and Harrison 2004; Robertson et al. 2004). An

improved response and overall survival were observed in patients receiving a dose of 500 mg IM compared to 250 mg IM.

Developing a SERD with better oral bioavailability that could overcome the dose limitation of fulvestrant is highly desired. However, challenges with such development have complicated the path. Despite the disclosure of several agents in the past (Lai et al. 2015; Weir et al. 2016; Guo et al. 2018; Hamilton et al. 2018; Tria et al. 2018), few have progressed into clinical testing and none have demonstrated activity in large randomized studies to date. Several of these challenges were associated with lack of competitive bioavailability to guide further development. However, recently, several small studies with heterogeneous group (variable prior therapies and presence or absence of ESR1 mutations) of patients with ER+/HER2- mBC reported promising activity (Bardia et al. 2017, 2019).

LY3484356 is an oral SERD. It is a potent degrader and selective pure antagonist of wild type and mutant estrogen receptor α (ERα or ESR1). LY3484356 potently inhibits transcription of ERα target genes such as PGR, GREB1, PDZK1, ARG, RASGRP1, and WISP2 in ER+ breast cancer cells. LY3484356 selectively inhibits the proliferation of ER+ breast cancer cell lines and has equivalent potency in both wild type and mutant ESR1 breast cancer cell lines. In in vivo target inhibition studies, LY3484356 has shown sustained and prolonged inhibition of gene expression of progesterone receptor, a transcriptional target of ERα that is measured as a PD biomarker in ESR1 wild type xenograft or ESR1 (Y537S) mutant patient-derived xenograft (PDX) tumor models in mice. The exposure in the tumors is 12 to 175× higher than plasma in mice. In in vivo efficacy studies, LY3484356 has demonstrated robust single-agent activity and tumor regressions in ESR1-wild type (MCF7, T47D, ZR-75-1, HCC1428) xenograft models and ESR1-mutant (Y537S) patient-derived xenograft models. LY3484356 is also brain penetrant and inhibits the growth of MCF7-fLuc breast cancer cells implanted orthotopically in the mouse brain.

LY3484356 is currently under evaluation in the EMBER trial (Phase 1a/1b Study of LY3484356 Administered as Monotherapy and in Combination with Anticancer Therapies for Patients with ER+ Locally Advanced or Metastatic Breast Cancer and Other Select Non-Breast Cancers). Phase 1a is a dose escalation of LY3484356 to determine the recommended Phase 2 dose (RP2D); followed by Phase 1b, randomized dose-expansion of LY3484356 as monotherapy and in combination with other anticancer therapies. Based on the totality of safety, PK and efficacy data from the EMBER study, the RP2D of LY3484356 was determined to be 400 mg once daily (QD).

CCI 134 patients received LY3484356 monotherapy in the EMBER (J2J-MC-JZLA) trial. Patients have received LY3484356 as monotherapy at each of the following daily doses: CCI
LY3484356 was well tolerated across dose levels in dose escalation, with no dose-limiting toxicities reported during the dose escalation and a maximum tolerated dose was not reached. The most frequently reported treatment-emergent adverse events (TEAEs) at the RP2D (CCI n=64) were nausea (CCI), fatigue (CCI), and diarrhea (CCI). Most TEAEs were Grade 1 or 2 in severity. Treatment-related adverse events (TRAEs) at the RP2D were observed in CCI patients, most frequently nausea (CCI), diarrhea (CCI), and fatigue (CCI . Two (CCI) patients treated at the RP2D required a dose reduction to

CCI CCI due to a TRAE (CCI). No dose reductions occurred at dose level.

CCI 45 female patients were enrolled in the EMBER-2 trial (J2J-MC-JZLB), and 2 dose levels (CCI) were evaluated in patients with early-stage breast cancer with a treatment period of 15 to 22 days. TEAEs were observed in CCI patients. Most TEAEs were Grade 1 or 2, with the most common TEAEs observed at each dose level CCI

Additional details can be found in the LY3484356 IB.

Window of opportunity trial designs in early stage breast cancer have been utilized to permit the evaluation of in vivo downstream effects of treatment with a specific compound with corresponding samples that otherwise might be difficult to obtain. Ultimately these presurgical studies provide insights into drug-mechanism of action, biologic effects, and dose-PD relationships in order to better inform the development of that drug in the clinic (Arnedos et al. 2019).

Measurement of ER modulation through an immunohistochemistry (IHC) assessment of change in percentage and intensity of ER staining by a H-score is clinically validated (Cohen et al. 2012). Indeed, the degree of target (ER) modulation of fulvestrant was successfully captured utilizing IHC-based assessments of change in both ER and progesterone receptor (PR) expression following treatments ranging from 2 to 6 weeks (Kuter et al. 2012; Robertson et al. 2013; Agarwal et al. 2016).

Change in Ki-67 expression following administration of standard or investigational preoperative endocrine therapy is also a well-established PD marker and study endpoint in clinical studies (Dowsett et al. 2011). The tumor cell proliferation protein, Ki-67, is validated as a prognostic and predictive biomarker in ER+ breast cancer (Stuart–Harris et al. 2008; Yerushalmi et al. 2010). Indeed, several trials have shown that the degree of suppression of Ki-67 correlates with clinical outcome, and that this change can be reliably assessed as early as 2 weeks after therapy initiation (Dowsett et al. 2011). Notably, short-term presurgical treatment with fulvestrant has also demonstrated measurable changes in Ki-67 (Agarwal et al. 2016; Kuter et al. 2012; Robertson et al. 2013).

Given the mechanism of action of LY3484356 as a degrader and pure antagonist of ER, an assessment of change in ER expression in tumor in response to LY3484356 treatment provides direct measurement of the PD modulation of the intended drug target.

Therefore, in this presurgical, window of opportunity study, the biological effects of 3 different doses of LY3484356 will be evaluated by measuring tumor changes in ER (primary endpoint), PR (secondary endpoint), and Ki-67 (secondary endpoint) in response to short term treatment with LY3484356. Additional parameters will include standard safety assessments and PK measurements along with exploratory analyses as detailed in Section 3.

2.3. Benefit/Risk Assessment

Selective estrogen receptor degraders as a class of drugs are promising given the demonstrated clinical activity and benefit of fulvestrant, currently the only approved SERD, in multiple large randomized studies. However, a need still exists to develop oral SERDs, such as LY3484356, with potentially improved bioavailability and enhanced biological activity.

The clinical safety experience of LY3484356 in advanced breast and endometrial cancer patients from the EMBER study is described in Section 2.2 with additional details described in the IB. LY3484356 monotherapy was well tolerated with the majority of observed AEs being low grade, reversible, monitorable and manageable, and the safety profile is consistent with that expected based on LY3484356 mechanism of action and the patient population being treated.

Nonclinical LY3484356 toxicology studies demonstrate an acceptable safety profile, with toxicities that are generally monitorable and/or reversible. CCI

Non-reproductive in vivo toxicology findings demonstrated partial to full reversibility after a 2-week recovery period (evaluated in rats). Female reproductive tract findings have similarly been observed with other approved agents, known to antagonize or degrade the ER, including tamoxifen and fulvestrant. To mitigate the risk of pharmacologically mediated reproductive and developmental toxicity, women of childbearing potential are not eligible for this study.

Potential toxicities will be regularly monitored during this study through ongoing assessment of patient symptoms, hematological and chemistry levels, and electrocardiogram (ECG) readings, as detailed in Section 8.2. Patients will also be advised to use sunscreen if out in direct sunlight, to reduce the possibility of phototoxicity.

In this study, LY3484356 will be administered for 15 days (-2 days to +7 days) to patients with early stage (I to III) ER+ breast cancer, awaiting a curative intent resection. This presurgical treatment course of LY3484356 is not expected to result in therapeutic benefit. However, given the short duration of treatment on this study and the lack of the additional mandatory research biopsies, for the majority of enrolled patients, the potential areas of concern for LY3484356 are

considered acceptable. More detailed information about the known and expected benefits and risks, SAEs, and reasonably anticipated AEs of LY3484356 can be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Determine PD effect of each dose level of LY3484356 on ER expression, in patients with ER+ early stage breast cancer.	• Change in ER expression (as measured by IHC and quantified by H-score) between pre- and on-treatment tumor samples, at each dose level of LY3484356
Secondary	
• Assess PD effect of each dose level of LY3484356 on Tumor cell proliferation.	• Change in Ki-67 (as measured by IHC and expressed by % positive scoring) between pre- and on-treatment tumor samples, at each dose level of LY3484356
• Assess PD effect of each dose level of LY3484356 on PR expression.	• Change in PR expression (as measured by IHC and quantified by H score) between pre- and on-treatment tumor samples, at each dose level of LY3484356
• Evaluate safety and tolerability of each dose level of LY3484356.	• Incidence of investigator assessed AEs) per NCI CTCAE v5.0, at each dose level of LY3484356
• Evaluate PK effect of each dose level of LY3484356.	• Plasma concentrations of LY3484356, at each dose level of LY3484356
Exploratory	
CCI	

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ER = estrogen receptor; IHC = immunohistochemistry; NCI = National Cancer Institute; PD = pharmacodynamics; PK = pharmacokinetic; PR = progesterone receptor.

4. Study Design

4.1. Overall Design

Study EMBER-2 is a Phase 1, open-label, randomized, pre-operative window study of LY3484356 in post-menopausal women with Stage I to III ER+, HER2- breast cancer who are scheduled for surgery with curative intent. Patients will consent to provide tumor samples obtained at the time of diagnosis and at the time of scheduled surgery or repeat biopsy, for the purpose of biomarker analyses. Patients will then be randomized to either 400 or 800 mg LY3484356 or directly assigned to the 200 mg dose (see table in Section 6.1) and receive LY3484356 for 15 days, up to and including the day of scheduled surgery or repeat biopsy (if neoadjuvant therapy is subsequently planned). Tumor samples taken pre- and on-treatment with LY3484356, at the time of diagnosis and scheduled surgery/repeat biopsy, respectively, will then be evaluated for biologic effects, as outlined in the study objectives. (See Section 8.8 for specifics regarding tumor tissue collections).

For the 400 and 800 mg doses, randomization will be stratified by tumor histology (infiltrating ductal carcinoma [IDC] versus infiltrating lobular carcinoma [ILC]; as locally determined from the diagnostic tumor biopsy). No stratification will occur for the 200 mg dose level.

A treatment window of 15 days (-2 to +7 days [ie, a range of 13 to 22 days of LY3484356 treatment] will be permissible to facilitate flexibility in scheduling of the on-treatment surgery/biopsy. The last dose of LY3484356 will be taken on the morning of surgery/biopsy.

The primary endpoint for this study is to determine change in ER expression (between pre- and on-treatment tumor samples) following LY3484356 treatment at each dose level. These changes will be measured utilizing an immunohistochemistry (IHC) H-score (0 to 300) that captures the change in the number of positive cells and intensity of ER staining.

Secondary endpoints include assessment of change in PR expression by IHC H-score (0 to 300); change in the percentage of Ki-67 staining positive tumor cells (Ki-67 index); and safety and tolerability and PK evaluation of LY3484356.

Taken together, these data will be used to describe the comparative biologic effects of each dose level of LY3484356 on early stage, treatment naïve ER+ breast tumors.

In addition, and in patients with sufficiently large tumors to permit additional sample provision for exploratory endpoint analyses, LY3484356 tumor biodistribution and further LY3484356 biologic effects (on ER and/or other cancer related biomarkers at both doses) will be evaluated at each dose level.

In the absence of toxicities, patients will remain on study treatment for a minimum of 13 days and until the day of surgery.

Please refer to Section 1.2 for a study schema.

4.1.1. Dose-Limiting Toxicity Definition

A DLT is defined as an AE that fulfills any 1 of the following DLT criteria from the Phase 1a/1b EMBER study of LY3484356 using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

- CTCAE ≥Grade 3 non-hematological toxicity. Exceptions will be made for:
  - Nausea, vomiting, diarrhea, or constipation that lasts for <72 hours and can be controlled with treatment and does not require hospitalization and
  - Grade 3 rash that resolves or improves to a Grade 2 or less within 7 days and remains tolerable may not be considered a DLT if agreed by the study investigator and Lilly clinical research physician (CRP)/clinical research scientist (CRS).
- Grade 4 neutropenia, anemia, or leukopenia of >7 days duration; anemia that requires packed red blood cell transfusion; or neutropenia that requires granulocyte-colony stimulating factor.
- Grade 4 thrombocytopenia of any duration or thrombocytopenia that requires platelet transfusion.
- Grade 3 thrombocytopenia with bleeding.
- Any febrile neutropenia.
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose-limiting (eg, any toxicity that is possibly related to the study medication that requires the discontinuation of LY3484356 during the approximately 15-day [+7/-2] treatment period).
- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5× the upper limit of normal (ULN), irrespective of baseline values
- ALT or AST ≥3×ULN and total bilirubin (TBL) ≥2×ULN (irrespective of baseline values)

Due to the short-term (15 days [+7/-2]) window of treatment with LY3484356, no dose modifications will be undertaken. If patients experience a DLT or AE as defined in Appendix 3 (Section 10.3), that is deemed dose limiting (eg, any significant toxicity possibly related to the study medication), per medical guidance and the opinion of the primary investigator, patients will discontinue LY3484356.

Ongoing and overall safety review will be performed by the study sponsor and the investigators. The rates of AEs and DLTs will be monitored in an ongoing basis as each patient enrolls. If at any time the cumulative incidence of either DLTs or AEs that result in postponement of the scheduled date of surgery (>1 day) is ≥20% (ie, the Bayesian posterior Pr (toxicity rate >20%)), patient accrual will be temporarily halted while a safety data review is triggered and a re-evaluation of dose may occur. Specifically, intermediate or lower doses may be explored in subsequently enrolled patients, that ensure patient safety while maintaining adequate target engagement.

4.2. Scientific Rationale for Study Design

The overall rationale for the study design is described in Section 2.1 (Study Rationale), Section 2.2 (Background), and Section 9 (Statistical Considerations). Dose selection and justification details can be found in Section 4.3 (Justification for Dose).

4.3. Justification for Dose

The clinical doses used in this study will be 200 mg, 400 mg, or 800 mg given orally once daily (see table in Section 6.1).

As outlined in Section 2.2 (Study Background), LY3484356 is under evaluation in the EMBER trial (Phase 1a/1b Study of LY3484356 Administered as Monotherapy and in Combination with Anticancer Therapies for Patients with ER+ Locally Advanced or Metastatic Breast Cancer and Other Select Non-Breast Cancers). Dosing, safety, PK, and efficacy data generated from the ongoing EMBER study forms the basis and justification for the doses used in this window of opportunity trial. Specifically, the clinical, PK, and pre-clinical PK observations described in Section 2.2 provide justification for the dose selection of 200 mg, 400 mg, and 800 mg.

The RP2D of LY3484356 has been determined as 400 mg. This pre-surgical pharmacodynamic trial permits evaluation of the biologic activity of LY3484356 at its RP2D (400 mg) and at the dose levels above (800 mg) and below (200 mg) the RP2D.

4.4. End of Study Definition

The end of the study is defined as the date of the last follow-up visit of the last global participant in the study as shown in the Schedule of Activities (SoA) (Section 1.3). Biomarker data will be evaluated on an interval batched basis. Upon evidence of evaluable primary and secondary endpoint data for 20 patients in each cohort, the study sponsor will have the option to end the trial.

5. Study Population

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

5.1. Inclusion Criteria

Age

(1) Participant must be at least 18 years of age.

Type of Participant and Disease Characteristics

(2) Histologically confirmed invasive breast carcinoma with the following characteristics:

a) Clinical Stage I to III according to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th Edition (Amin et al. 2017).
b) Primary tumor measuring ≥1 cm in largest diameter by ultrasound.
c) ER+ (>50% of tumor cell nuclei from the invasive component, that is immunoreactive by immunohistochemistry or Allred Score >5 [Harvey et al.1999]), and HER2- (according to American Society of Clinical Oncology (ASCO)/Clinical Practice Guideline (CAP) guidelines for HER2 testing [Wolff et al. 2018]), per local laboratory tumor testing.
d) Deemed appropriate for curative surgical resection.
e) Multifocal disease is allowed if confined to 1 breast, and if each tumor is ER+, HER2- and at least 1 tumor is ≥1 cm.

(3) Participant may be scheduled for definitive neoadjuvant therapy after participating in this study but must be willing to undergo a biopsy for Day 15 of study tissue collection (as specified in Section 1.3 and Section 8.8), before commencing subsequent neoadjuvant therapy.

(4) Participant must be willing and able to provide pre- and on-treatment tumor samples, as specified in Section 1.3 and Section 8.8.

(5) Have a performance status of 0 or 1 on the ECOG scale (Oken et al. 1982).

(6) Have adequate organ function, as defined in the table below:

System	Laboratory Value
Hematologic	
ANC	$\geq 1.5\times10^9$/L
Platelets	$\geq 100\times10^9$/L
Hemoglobin	≥8 g/dL

Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.
Note: Transfusions to increase a patient's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug.

Hepatic	
Total bilirubin	≤1.5×ULN, patients with Gilbert's syndrome with a total bilirubin ≤3.0 times ULN and direct bilirubin within normal limits are permitted.
Serum albumin	≥ 3g/dL
ALT and AST	≤2.5×ULN
Renal	
Serum creatinine **OR** Measured creatinine clearance **OR** Calculated creatinine clearance	<1.5×ULN **OR** ≥50 mL/min/1.73 m^2

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal.

(7) Participants must be able to swallow capsules.
(8) Are able and willing to be available for the duration of the study and are willing to follow study procedures.

Sex

(9) Participants must be female.
(10) Postmenopausal women due to the natural cessation of ovarian function, surgery, or therapeutic radiation, defined by at least 1 of the following criteria:

a) Prior bilateral oophorectomy, or
b) Age ≥60 years, or
c) Age <60 years, amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression), and follicle-stimulating hormone and estradiol levels in the postmenopausal range.

Informed Consent

(11) 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

(12) Bilateral invasive breast cancer.
(27) Occult primary breast cancer.
(13) Metastatic breast cancer (local spread to axillary or internal mammary lymph nodes is permitted).

(14) Inflammatory breast cancer, defined as the presence of erythema or induration involving one third or more of the breast (Hortobagyi et al. 2017).
(15) Plan to receive concurrent neoadjuvant therapy with any other nonprotocol anti-cancer therapy.
(16) Prior therapy (of any kind) for an invasive or non-invasive breast cancer (ductal carcinoma in situ or lobular carcinoma in situ).
(17) Prior radiotherapy to the ipsilateral chest wall for any malignancy.
(18) Prior anti-estrogen therapy with raloxifene, tamoxifen, aromatase inhibitor, or other selective estrogen receptor modulator, either for osteoporosis or prevention of breast cancer.
(19) Prior hormone-replacement therapy within 4 weeks of the start of study treatment.
(20) Have a serious concomitant systemic disorder (eg, active infection or a gastrointestinal disorder causing clinically significant symptoms such as nausea, vomiting, diarrhea, or profound immune suppression) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol, including but not limited to the following:

a) Have uncontrolled human immunodeficiency virus (HIV) 1/2 infection. Controlled HIV infection is defined as:

(i) Compliance with highly active anti-retroviral therapy

(ii) No evidence of autoimmune deficiency syndrome-defining opportunistic infections within the last 2 years
(iii) CD4 count >350 cells/μL, and
(iv) Required anti-retroviral therapy is not prohibited based on predicted dose-dose interactions with investigational medical product (see Section 6.5).

b) Active hepatitis B or C virus infection (screening required).
c) Severe renal impairment, interstitial lung disease (ILD), severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhea.

(21) Have a serious cardiac condition, such as

a) Congestive heart failure
b) New York Heart Association Class III/IV heart disease
c) Unstable angina pectoris
d) Myocardial infarction within the last 3 months
e) Valvulopathy that is severe or moderate, or deemed clinically significant
f) Arrhythmias that are symptomatic or require treatment (not including patients with rate-controlled atrial fibrillation)
g) Cerebrovascular accident (stroke) within the last 3 months
h) A mean QT interval corrected for heart rate of ≥470 msec on screening ECG, as calculated using the Fridericia's formula at several consecutive days of assessment

i) Baseline bradycardia with resting heart rate <60 beats per minute

(22) Have had major surgery within 28 days prior to randomization to allow for post-operative healing of the surgical wound and site(s).

(23) Criterion (23) has been removed.

(24) Known allergic reaction against any of the components of the study treatment.

(28) Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.

Prior/Concurrent Clinical Study Experience

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

(26) Have participated, within the last 30 days (3 months for studies conducted in the United Kingdom), in a clinical study involving an investigational product. If the previous investigational product has a known long half-life, 5 half-lives or 30 days (3 months for studies conducted in the UK), whichever is longer, should have passed.

5.3. Lifestyle Considerations

Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products and avoid medications considered to be strong inducers and inhibitors of cytochrome P450 3A4 (CYP3A4), P-glycoprotein 1 (P-gp), and uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) (see examples in Appendix 6, Section 10.5) while on study and 2 weeks prior to the start of LY3484356, which is an in vitro substrate of CYP3A4, P-gp and UGT1A1.

Caution should be used with concomitant medications that are sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, or substrates of these CYPs with a narrow therapeutic index.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

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

6. Study Intervention

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

6.1. Study Intervention(s) Administered

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

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/study site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- returning all unused medication at the end of the study to Lilly, or its designee, unless Lilly and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law
- Patients enrolled in this Phase 1 open-label, randomized, pre-operative study will receive LY3484356 at one of the dose levels, shown in the table below.
- Patients will start LY3484356 on Day 1 and continue it daily, up to and including the day of surgery or repeat biopsy on Day 15 (-2 to +7 days).
- Doses will be administered at approximately the same times on each day. Patients should not consume any food at least 1 hour before and at least 2 hours after administration of LY3484356.

Study Drug	Cohort	Proposed Doses	Dose Schedule, Route of Administration, Duration
LY3484356	A	400 mg	QD, PO, administered for 15 days[a]
LY3484356	B	800 mg	QD, PO, administered for 15 days[a]
LY3484356	C	200 mg	QD, PO, administered for 15 days[a]

Abbreviations: PO = orally; QD = once daily.

[a] Allowable window to facilitate scheduling of on-treatment surgery/biopsy: Day 15 (- 2 to + 7 days, [a range of 13 to 22 days of LY3484356 treatment will be permissible]). Patients should continue to dose study drug continuously through the day of surgery/biopsy, with the last dose of LY3484356 administered on the morning of surgery/biopsy.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature 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 and only authorized site staff may supply 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 site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, 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.
5. Investigators should consult the site training, Pharmacy Manual, or label for specific study drug information.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study that will implement a 1:1 randomization design for the 400 mg and 800 mg to mitigate the selection bias in allocating patients to each dose level of LY3484356. For the 200 mg cohort, no randomization will occur, as this cohort will open once the 400 mg and 800 mg cohorts are closed.

Randomization will be stratified by tumor histology (IDC versus ILC versus Other; as locally determined from the diagnostic tumor biopsy) to ensure appropriate distribution of these histologies across each dose level cohort.

6.4. Study Intervention Compliance

Patient compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and by counting returned tablets and/or capsules. Patients must receive 80% of assigned doses to be considered compliant with study. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

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

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

CYP Substrates

In vitro assays indicated that LY3484356 is a time-dependent inhibitor of CYP2C8, CYP2C9, CYP2C19, and CYP3A. LY3484356 is also predicted to be a clinically relevant reversible inhibitor of CYP2B6, CYP2C19, CYP2C8, CYP2C9, and CYP2D6. As a result, caution should be used with concomitant medications that are sensitive substrates of CYP2B6, CYP2C8,

CYP2C9, CYP2C19, CYP2D6, and CYP3A4, or substrates of these CYPs with a narrow therapeutic index. A week of washout time following LY3484356 treatment is advised before starting sensitive substrates of CYP2C8, CYP2C9, CYP2C19, and CYP3A (Section 10.5 Appendix 5, Section 10.6 Appendix 6, and Section 10.7 Appendix 7).

UGT1A1, P-gp and BCRP

According to preclinical studies, UGT1A1 is involved in the metabolism of LY3484356. As a precaution, strong inducers and inhibitors of UGT1A1 should be avoided (Section 10.8 Appendix 8).

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

Consult the IB for additional information.

6.5.1. Photosensitivity

Based on an in vitro study, exposure to LY3484356 may result in photosensitivity. Patients are advised to avoid direct sun exposure and the use of tanning beds during study administration period and at least 5 days after the last dose. If patients must be exposed to the sun, they should be advised to wear sunscreen, appropriate sun-blocking clothing, and sunglasses.

6.6. Dose Modification

Due to the short-term (15 days [+7/-2]) window of treatment with LY3484356, no dose modifications will be accepted. If any AEs as defined in Appendix 3 (Section 10.3) are deemed as dose limiting (eg, any significant toxicity possibly related to the study drug) per medical guidance and the opinion of the primary investigator, the recommendation will be to discontinue LY3484356.

6.7. Intervention after the End of the Study

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

6.7.1. Treatment after Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, which will be performed no more than 3 months after the last patient is randomized/enrolled. Investigators will continue to follow the SoA (Section 1.3) for all patients until notified by Lilly that study completion has occurred.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Possible reasons leading to permanent discontinuation of investigational product:

- Subject decision
  - the participant or the participant's designee (eg, parents or legal guardian, requests to discontinue investigational product).
- The patient is significantly noncompliant with study procedures and/or treatment.
- Unacceptable toxicity or DLT toxicity requiring dose discontinuation.
- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent.
- The investigator decides that the patient should be discontinued from study treatment.

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

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:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor Clinical Research Physician (CRP) agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact 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

- Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.
- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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

Not applicable.

8.2. Safety Assessments

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

8.2.1. Electrocardiograms

Electrocardiograms are to be single ECGs as indicated in the SoA (Section 1.3).

8.2.2. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or during the short-term follow-up period after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.2.1. Hepatic Safety Monitoring

Liver testing (Appendix 4, Section 10.4), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine phosphokinase, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

- ALT or AST ≥5× ULN (irrespective of baseline values)
- ALT or AST ≥3× ULN and total bilirubin (TBL) ≥2× ULN (irrespective of baseline values)

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

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

Additional Hepatic Safety Collection

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

- ALT or AST ≥5× ULN (irrespective of baseline values)

- ALT or AST ≥3× ULN and total bilirubin (TBL) ≥2× ULN (irrespective of baseline values)

In all study participants:

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

8.2.3. Safety Surveillance

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

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

In addition to annual periodic safety updates and to further inform investigators, a line listing reports of suspected unexpected serious adverse reactions is created and distributed to investigators on a twice-yearly) basis. Any significant potential risk/safety concerns that are being monitored, as well as any results being reported in other periodic reports for the compound, SAC decisions, and other significant safety data (for example, nonclinical, clinical findings, and removal of SARs) are included in the report.

8.3. Adverse Events and Serious Adverse Events

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

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

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

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

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF. Although all AEs, after signing of the ICF, are recorded by the site in the CRF/electronic data entry, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving LY3484356, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

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

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a 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 Adverse Events and Serious Adverse Events

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 non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and adverse events of special interest (AESI; 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 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Not applicable.

8.3.6. Events or Outcomes

Not applicable.

8.3.7. Adverse Events of Special Interest

Not applicable.

8.3.8. Complaint Handling

Lilly collects product complaints on investigational products 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.

8.4. Treatment of Overdose

Refer to the IB of LY3484356 for available information on the signs, symptoms, and treatment of overdose.

8.5. Pharmacokinetics

- Venous blood and tumor samples will/may be collected for measurement of plasma/tumor concentrations of LY3484356 as specified in the SoA (Section 1.3).
- Samples may be removed or collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last participant visit for the study.

8.6. Pharmacodynamics

Samples collected to measure PD biomarkers will be identified by the participant number (coded) and retained at a facility selected by Lilly or its designee for a maximum of 15 years following last participant visit for the study at a facility selected by Lilly or its designee. See Section 8.8 for biomarker information.

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3484356 and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy. Samples may be used to determine the somatic or germline origin of tumor-associated genetic alterations.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or Ethical Review Boards (ERBs)/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3484356 or after LY3484356 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section. Samples may also be used to determine the somatic or germline origin of tumor-associated genetic alterations.

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid, ribonucleic acid, proteins, lipids, and other cellular elements.

Breast tumor tissue and plasma samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow. It is recommended that the cold ischemia time be kept to 1 hour or less for all tissue specimens as per the ER and PgR IHC Testing Guideline recommendations (ASCO/CAP; Yildiz-Aktas et al. 2012).

Collection of the following tumor tissue samples are requested for all patients in order to participate in this study:

1. Pre-treatment (Required)

- **Archival tissue** from a diagnostic tumor biopsy will be sufficient provided it was taken no more than 6 weeks prior to consent.
    - The tumor block or a total of 20 unstained slides should be submitted along with a copy of the pathology report confirming viable tumor sufficient to make the diagnosis, along with the requisite biomarker profile (ER+, HER2-) for eligibility outlined in Section 5.1.
        - If the diagnostic tumor block is close to exhaustion, case by case consideration will be given after consultation with the CRP or CRS to accept less than 20 unstained slides.
- **Fresh on-study biopsy** (*16-gauge core needle or wider is suggested with a minimum of 3 cores obtained*) performed prior to treatment initiation, will be:
    - Required: If archival tissue unavailable/exhausted or was collected >6 weeks prior to consent, or while on Hormone Replacement Therapy
    - Optional: For the purpose of Oncotype DX testing, at the treating physician's discretion.
    - Cores 1 through 3 are to be Formalin-Fixed

2. On-treatment (Required)

- Tumor tissue can be obtained either from:
    - A **Core needle biopsy** (*16 gauge or wider is suggested with a minimum 4 cores obtained*), if the patient is scheduled for subsequent neoadjuvant therapy.
        - Cores 1 through 3 are to be Formalin-Fixed
        - Core 4 is to be flash frozen with the weight of this core recorded where possible.
    - The **resected surgical specimen** in patients scheduled directly for surgery.
        - Standard local pathology practices will be acceptable. Surgical specimens need to be placed in formalin immediately following gross inspection and tissue procurement.
        - Following completion of the surgical pathology report the tumor block or a total of 20 unstained slides should be submitted along with a copy of the pathology report confirming viable tumor sufficient to make the diagnosis.

2.1 On-treatment (Optional but strongly encouraged)

- For sufficiently large tumor resection specimens (deemed to contain sufficient tumor for research purposes), the following samples should be obtained where possible.
    1. Tumor sample and a sample of adjacent normal tissue from the resection specimen of at least 0.5 cm^3 each, for immediate flash freezing to support PK assessment. Importantly, the weight of each specimen should be recorded prior to freezing.

2. Tumor sample and a sample of adjacent normal tissue of approximately 0.5 cm×0.5cm each, to be immediately placed in formalin tissue block for exploratory research.

As described above, unstained archival tumor tissue sample of sufficient quantity and quality must be confirmed by the site to be available to allow for retrospective central ER, PR, and Ki-67 assessments. Due diligence should be used to ensure that sample contains sufficient viable tumor cells (not a normal adjacent or a tumor margin sample) prior to shipment to central laboratory.

All accompanying pathology reports must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission.

Sponsor/Lilly has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

This study will analyze biomarkers relevant to LY3484356, mechanism of action of LY3484356, the variable response to study drug, tumor cell biology, immune function, tumor microenvironment, angiogenesis, and pathways associated with cancer. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3484356 or after LY3484356 becomes commercially available.

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

It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described above in this biomarker section.

8.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization parameters and Health Economics will not be evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

No formal statistical hypotheses and no formal statistical hypothesis testing will be performed.

9.2. Sample Size Determination

Approximately 90 participants will be assigned equally to the different dose-level cohorts in this study to ensure that conservatively 20 participants, with evaluable biomarker data are ultimately available for analysis from each cohort. The sponsor may elect to continue accrual until sufficient biomarker data is generated. Participants will be randomized to either 800 mg or 400 mg once daily oral dosing, or directly assigned to the 200 mg dose. See details about randomization in Section 6.3.

CCI [redacted]

9.3. Populations for Analyses

The following analysis sets will be defined for this study:

Intention-to-Treat (ITT) analysis set: will include all enrolled/randomized participants. The ITT analysis of biomarker data will consider allocation of participants to treatment groups as assigned/randomized and not by actual treatment received. This analysis set will be used for all baseline and post-treatment analyses.

Safety analysis set: will include all enrolled/randomized participants who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a participant actually received, regardless of the participant's cohort assignment. The safety analysis set will be used for all dosing/exposure and safety analyses.

Pharmacokinetic analysis set: will include all enrolled/randomized participants who received at least 1 full dose of LY3484356 and have at least 1 postbaseline evaluable PK sample.

Biomarker analysis set: will include the subset of participants from the ITT analysis set from whom a valid assay result has been obtained.

9.4. Statistical Analyses

9.4.1. General Considerations

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

All CIs will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis

methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.2. Primary Objective Analysis

Change in ER expression is defined as the change from the pre-treatment to on-treatment sample. The geometric mean of change in the ER H-score, the percent change in H-score of ER expression, and the 90% CI (based on t statistic) will be summarized for each cohort.

9.4.3. Secondary Objectives Analyses

Change in Ki-67 index is defined as the change from the pre-treatment to on-treatment. The geometric mean of change in Ki-67 expressing positive cells, the percent change in Ki-67 expressing positive cells, and its 90% CI (based on t statistic) will be summarized for each cohort, per international guidelines (Dowsett et al. 2011). Subgroup analyses will be performed in patients with higher (>5%) baseline Ki-67%.

Change in PR expression is defined as the change from the pre-treatment to on-treatment. The geometric mean of change in the ER H-score, the percent change in H-score of PR expression, and the 90% CI (based on t statistic) will be summarized for each cohort.

9.4.4. Safety Analyses

All participants who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

Safety analyses will include summaries of

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

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Plasma and tumor concentrations of LY3484356 will be summarized.

In addition, PK parameter estimates for LY3484356 may be calculated by population PK analysis methods using NONMEM, data allowing.

Pharmacokinetic/PD analyses may be conducted to explore exposure-response relationships between LY3484356 concentrations in systemic circulation and various PD measures as a second step if the dose-response relationship is positively assessed.

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/randomized in the study, treated in the study, completing the study (patients who complete the required treatment period), and discontinued from the study (overall and by reason for discontinuation).

9.4.6.2. Participant Characteristics

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

9.4.6.3. Concomitant Therapy

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

9.4.6.4. Treatment Compliance

The number of doses received, dose omissions, dose reductions, and dose intensity will be summarized for all treated participants by dose/treatment cohort.

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

9.5. Interim Analyses

No interim analyses are planned for this study. However, each cohort will be continuously monitored for safety. Enrollment to a cohort will be temporarily halted and a safety data review will be triggered CCI [redacted]

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for
  - 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, and
  - providing oversight of the conduct of the study at the site 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.

10.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.2. 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.

10.1.3. Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Lilly and international policies.

10.1.4. 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 (eg, 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 (eg, 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 (eg, Contract Research Organizations).

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

Data Capture System

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

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

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

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

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

10.1.5. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be

explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.6. Study and Site Start and Closure

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

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

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

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

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

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

- If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (eg, blood pressure increased, neutrophils decreased, etc.) and it is associated to a diagnosis of an AE, then the AE should be entered in the CRF.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either 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 the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF. Discrepancies between local and central laboratory results will not be considered protocol deviations.
- 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.

Investigators must document their review of each laboratory safety report.

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Leukocytes (WBC)	**Serum Concentrations of:**
Neutrophils[b]	Alanine aminotransferase (ALT)
Lymphocytes	Albumin
Monocytes	Alkaline phosphatase
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Bilirubin, direct
Erythrocytes (RBC)	Bilirubin, total
Hemoglobin (HGB)	Blood urea nitrogen (BUN) or blood urea
Hematocrit (HCT)	Calcium
Platelets (PLT)	Creatinine
	Glucose (random
Urinalysis[b]	Potassium
Blood	Protein
Glucose	Sodium
Ketones	
pH	**Coagulation**[b]
Protein	PT/INR
Specific gravity	aPTT
Urine leukocyte esterase[c]	
Blood Tests[a,b]	

Hepatitis B surface antigen

Hepatitis C antibody

Follicle Stimulating Hormone (FSH)
Estradiol

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

[a] Treatment and enrollment decisions will be based on local laboratory results.

[b] Local or investigator-designated laboratory.

[c] Urine microscopy may be used in place of the urine leukocyte esterase assessment to test for the presence of WBC.

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

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 patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

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

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

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

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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 use CTCAE v5.0 (NCI 2018) to assign AE severity grades.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it

is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SAE form.
SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor. • 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: Liver Safety: Suggested Actions and Follow-up Assessments

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

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

- **For testing selected, analysis is required to be completed by the Lilly designated central laboratory except for Microbiology.**
- **Local testing may be performed in addition to central testing when required for immediate patient management.**
- **Results will be reported if a validated test or calculation is available.**

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

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

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

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

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

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

[d] Assayed by Investigator-designated local laboratory ONLY; no Central Testing available.

10.5. Appendix 5: Inducers and Strong Inhibitors of CYP3A

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

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

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

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

10.6. Appendix 6: CYP3A Sensitive Substrates

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

abemaciclib	lomitapide
acalabrutinib	lopinavir
alectinib	lovastatin
alfentanil	lumefantrine
aprepitant (also fosaprepitant)	lurasidone
atazanavir	maraviroc
atorvastatin	midazolam
avanafil	midostaturin
avapritinib	naloxegol
bosutinib	neratinib
brotizolam	nisoldipine
budesonide	paritaprevir
buspirone	quetiapine
cobimetinib	quinidine
conivaptan	saquinavir
darifenacin	sildenafil
darunavir	simeprevir
dasatinib	simvastatin
dronedarone	sirolimus
ebastine (OUS only)	tacrolimus
elighlustat	ticagrelor
elvitegravir	tipranavir
entrectnib	tolvaptan
eplerenone	triazolam
everolimus	ulipristal
felodipine	uprogepant
ibrutinib	vardenafil
indinavir	venetoclax
isavuconazole (prodrug is isavuconazonium sulfate)	vinblastine
ivabradine	zanubrutinib
ivacaftor (also ivacaftor with lumacaftor, ivacaftor with tezacaftor)	

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

10.7. Appendix 7: Other CYP-sensitive Substrates

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

	Sensitive substrates
CYP2C8	repaglinide
CYP2C9	celecoxib
CYP2C19	S-mephenytoin, omeprazole
CYP2D6	atomoxetine, desipramine, dextromethorphan , eliglustat(e), nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine

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

10.8. Appendix 8: Examples of strong clinical inhibitors and inducers for UGT1A1

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

	Inhibitors	Inducers
UGT1A1	ombitasvir and paritaprevir and ritonavir and dasabuvir, faldaprevir	telaprevir

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

Note: Strong inhibitors and inducers are drugs that demonstrate alterations in AUC of ≥2-fold with a UGT1A1 substrate in clinical DDI studies and/or pharmacogenetics data.

10.9. Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed Consent

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

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

Changes in Study Conduct During Exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.
Other alternative locations: Procedures that may be done at an alternate location in exceptional circumstances.

Data captures

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

Safety reporting

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

Return to on-site visits

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

Study intervention and ancillary supplies (including participant diaries)

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

These requirements must be met before action is taken:

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

Adjustments to visit windows

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

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

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, 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 at alternate locations

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

10.10. Appendix 10: Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CAP	Clinical Practice Guideline
CI	confidence interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
DLT	dose-limiting toxicity
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ER+	estrogen receptor-positive
ERα	estrogen receptor α
EDC	electronic data capture system
ERB	Ethical Review Board
G	grade
HER2-	human epidermal growth factor receptor 2 negative

Term	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDC	infiltrating ductal carcinoma
IEC	Independent Ethics Committee
ILC	infiltrating lobular carcinoma
IM	intramuscular
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
mBC	metastatic breast cancer
NCI	National Cancer Institute
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
P-gp	P-glycoprotein 1
PK/PD	pharmacokinetics/pharmacodynamics
PR	progesterone receptor
SAE	serious adverse event
SAR	serious adverse reaction

Term	Definition
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.
SERD	selective estrogen receptor degrader
SoA	Schedule of Activities
TBL	total bilirubin
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal

10.11. Appendix 10: Protocol Amendment History

Amendment (a)

This amendment is considered to be not substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment incorporates changes to address feedback from the Voluntary Harmonisation Procedure for Clinical Trials of Medicinal Products. In addition, this amendment includes changes made to correct and clarify information for sites. This amendment also corrects typographical errors and inconsistencies that were noted in the JZLB protocol.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities Biomarker Plasma	Biomarker plasma to be collected	To better understand the mutational burden of early stage disease and whether changes occur with study drug administration
1.3. Schedule of Activities Vital Signs	More details about how to collect vital signs for Visits 1 and 2	To provide guidance on when vital signs are to be collected
1.3. Schedule of Activities ECG	Additional ECG added 3-4 hours after dose at Visit 1	To provide clarity on need for additional ECG collection timepoint
1.3. Schedule of Activities Follicle Stimulating Hormone/estradiol	Added collection for patients less than 60	To align with inclusion criterion 10
1.3. Schedule of Activities Hepatitis B & C	Added testing for screening for hepatitis B & C	To align with requirement that patients with hepatitis B & C be excluded from trial
1.3. Schedule of Activities Surgical Pathology Report	Added that this is only required for patients who provide surgical resection for on-treatment tissue collection.	To clarify that only some patients will be required to do this
1.3. Schedule of Activities Patient diary	Collection of diary can occur at visit 3 or visit 4	To provide flexibility
4.1.1. Dose Limiting Toxicities 8.2.2.1. Hepatic Safety Monitoring Additional Hepatic Safety Collection	Changed levels of ALT or AST that qualify as a DLT	To satisfy concerns about hepatic safety

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria Criterion 20 iv.	Changed to say hepatitis B&C testing is required	To align with requirement that patients with hepatitis B & C be excluded from trial
5.2. Exclusion Criteria Criterion 23	Deleted criterion 23: "Pregnant, breastfeeding, or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 180 days after the last dose of study medication"	Because only post-menopausal women can be in the study, this criterion was considered unnecessary and deleted
5.2. Exclusion Criteria Criterion 25	Added new criterion that occult breast cancer is not allowed	To clarify that patients with occult breast cancer are not eligible for the study
5.3. Lifestyle Considerations 6.5. Concomitant Medications	Added and uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) added to substances to avoid while on study medicine	In vitro, UGT enzymes were shown to be involved in the metabolism of LY3484356
5.4. Screen Failures	Added that any participant who does not meet enrollment criteria and was inadvertently enrolled will be discontinued from study treatment and safety follow up should be performed.	So that this process applies to all participants
6.3. Measures to Minimize Bias: Randomization and Blinding	Added "other" to tumor histology stratification	To give more information about the randomization process, included "other" histology as a third stratification level
6.5. Concomitant Medications 10.7. Appendix 8: Other CYP-sensitive Substrates	CYP2B6 added to list of substances to be cautious with	LY3484356 reversibly inhibits the metabolism of CYP2B6
6.5.1. Photosensitivity	Added more guidance about sun avoidance	To help ensure investigators and participants are aware of this risk and to provide guidance on how to manage the risk
7.2. Participant Discontinuation/Withdrawal from the Study	Removed pregnancy as reason for withdrawal	Because only post-menopausal women can be in the study, this statement was considered unnecessary and deleted
8.8. Biomarkers	Plasma collection added	To better understand the mutational burden of early stage disease and whether changes occur with study drug administration

Section # and Name	Description of Change	Brief Rationale
9.5. Interim Analysis	Addition of >50%	To remedy an accidental deletion and match the SAP
10.2. Appendix	Inclusion of additional blood tests	To clarify these blood tests should be conducted as part of Eligibility confirmation
10.1.1.	Removed need for rescreened patients to sign new ICF	Rescreening is not permitted in this study
10.5.1. Discontinuation of Inadvertently Enrolled Patients in the United Kingdom	Deleted	So that this process applies to all participants
10.8. Appendix 8: Clinical inhibitors for P-gp 10.9. Appendix 9: Examples of strong clinical inhibitors and inducers for UGT1A1 (Aug 2020)	Addition of tables for conmeds	To add more information about conmeds

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