Protocol J2J-MC-JZLE(b)

An Open-label, Two-part Study of the Disposition and Absolute Bioavailability of [^{14}C]-LY3484356 in Healthy Females of Non-Childbearing Potential

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Approval Date: 05-Aug-2021

Title Page

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Protocol Number: J2J-MC-JZLE

Amendment Number: (b)

Compound: LY3484356

Study Phase: 1

Short Title: Two-part Study of the Disposition and Absolute Bioavailability of [^{14}C]-LY3484356

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number

IND: 145311

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 05-Aug-2021 GMT

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	25-May-2021
Protocol Amendment (a)	25-June-2021

Amendment (b)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Level of detail in study rationale reduced	For clarity
1.1. Synopsis; 3. Objectives and Endpoints	Part 1 and Part 2 objectives split out into separate tables	For readability
2.2. Background	Level of detail reduced	For readability
2.3. Benefit/Risk Assessment	Text structure updated	For readability
5.4. Screen Failures	Interval between re-screenings updated	For clarity
8.6. Pharmacokinetics	Text updated to reflect blood volume sampling requirements	For clarity
8.6.1. Bioanalysis	Vendor for plasma profiling and plasma metabolite identification added	For accuracy
Appendix 2 (Section 10.2.1.)	Part 2: blood sampling volumes amended following feedback from analysis vendors	For accuracy

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: An Open-label, Two-part Study of the Disposition and Absolute Bioavailability of [^{14}C]-LY3484356 in Healthy Females of Non-Childbearing Potential

Short Title: Two-part Study of the Disposition and Absolute Bioavailability of [^{14}C]-LY3484356

Rationale: Study J2J-MC-JZLE (JZLE) is a Phase 1 open-label, 2-part study of LY3484356 containing [^{14}C]-LY3484356 administered to healthy females of non-childbearing potential.

Part 1 of this study determines the disposition of [^{14}C]-LY3484356 and identifies the metabolites present in plasma, urine, and feces following a single oral administration of LY3484356 containing [^{14}C]-LY3484356 as a solution. This study will provide understanding of the clearance pathways of LY3484356 in humans, which is important to assess the likelihood of effects of renal or hepatic impairment on the disposition of LY3484356 and the likelihood for drug-drug interactions (DDIs) with LY3484356. Furthermore, knowledge of the metabolism and elimination of parent drug and its metabolites and major circulating metabolites is useful for evaluating needs of metabolite(s)-mediated DDI studies and metabolite(s) in safety testing requirements elucidated in the Food and Drug Administration Guidance and International Conference on Harmonisation M3.

Part 2 of this study determines the absolute bioavailability of LY3484356 of a tablet formulation in humans using an intravenous (IV) microtracer of [^{14}C]-LY3484356 (containing CCI radioactivity). Absolute bioavailability information aids quantitative evaluation of drug disposition of LY3484356.

Objectives and Endpoints:

Part 1

Objectives	Endpoints
Primary	
• To determine the disposition of radioactivity in healthy nonchildbearing women following oral administration of a single dose of CCI [^{14}C]-LY3484356	• Urinary and fecal excretion of total radioactivity over time expressed as a percentage of the total radioactive dose

Secondary	
• To determine the pharmacokinetics (PK) of total radioactivity and LY3484356 in plasma following a single oral dose of CCI [^{14}C]-LY3484356	AUC(0-∞) and C_{max} for radioactivity and LY3484356 in plasma
• To assess the mass balance by quantifying radioactivity excretion in urine, feces, and expired air (if applicable)	• Total radioactivity recovered in urine, feces, and expired air (if applicable)
• To identify metabolites of LY3484356 in plasma, urine, and feces	• Total number of metabolites and identification of metabolites
• To assess the safety and tolerability of a single dose of CCI [^{14}C]-LY3484356 (containing 100 µCi) in healthy nonchildbearing women	• A summary of TEAEs

Part 2

Objectives	Endpoints
Primary	
• To determine the absolute bioavailability of LY3484356 following a single oral dose of CCI of LY3484356 along with an IV dose of CCI of [^{14}C]-LY3484356 CCI	• absolute bioavailability (F) of LY3484356
Secondary	
• To evaluate the PK of LY3484356, [^{14}C]-LY3484356 and total radioactivity following oral dosing of LY3484356 and IV dosing of [^{14}C]-LY3484356	• AUC(0-∞) and C_{max} for total radioactivity, [^{14}C]-LY3484356 and LY3484356 in plasma
• To assess the safety and tolerability of LY3484356 following a single oral dose of CCI LY3484356 along with an IV dose of CCI of [^{14}C]-LY3484356 CCI in healthy nonchildbearing women	• A summary of TEAEs

Overall Design:

Screening (Part 1 and Part 2)

All participants will be screened within 28 days prior to enrollment.

Treatment and Assessment Period

Part 1:

Participants will be admitted to the Clinical Research Unit (CRU) on Day -1. On the morning of Day 1, following an overnight fast of at least 10 hours, participants will receive a single oral dose of CCI of [^{14}C]-LY3484356 CCI administered as an oral solution.

Participants will be discharged from the CRU as early as Day 12 and up to Day 22, provided recovery of radioactivity has reached the following threshold values:

- ≥90% of the radioactive dose is recovered, and
- ≤1% of the radioactive dose per day is recovered in excreta (urine and feces combined) for 2 consecutive days on which a fecal sample is collected.

Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the sponsor and investigator (or designee).

For participants experiencing emesis within 4 hours following ^{14}C dosing, vomitus will be collected. Attempts will be made to collect vomitus from participants experiencing emesis after 4 hours post dose. All vomitus will be collected and stored for possible analysis as deemed appropriate.

Part 2:

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, following an overnight fast of at least 10 hours, participants will receive a single oral dose of CCI of LY3484356 as CCI tablets and followed CCI by a single dose of CCI of [^{14}C]-LY3484356 (containing CCI of radioactivity [microtracer]) administered as approximately a CCI IV infusion. Participants will remain resident in the CRU until Day 9.

During the infusion and for at least 2 hours post-infusion, the blood samples will be taken from the arm contra-lateral to the infusion site.

Follow-up (Part 1 and Part 2)

Participants will receive a follow-up call approximately 7 days after clinic discharge.

Disclosure Statement: This study is an open-label, 2-part, disposition and absolute bioavailability study of [**^{14}**C]-LY3484356 in healthy females with non-childbearing potential at a single Phase 1 Clinical Research Unit (CRU).

Number of Participants: In Part 1, it is planned that up to 6 participants may be enrolled to ensure that at least 4 participants complete the study or have evaluable PK data; in Part 2, it is planned that up to 8 participants may be enrolled to ensure that at least 6 participants complete the study or have evaluable PK data for both treatments (oral and IV). Participants in Part 1 will

not participate in Part 2, nor will participants in Part 2 participate in Part 1. Part 1 and Part 2 are independent of each other and do not need to be conducted in sequential order.

Intervention Groups and Duration: Participants in Part 1 participate in 1 treatment period. Participants in Part 1 will be screened within 28 days prior to enrollment and will receive a single oral dose of CCI of [^{14}C]-LY3484356 (containing CCI).

Participants in Part 2 will participate in 1 treatment period. Participants in Part 2 will be screened within 28 days prior to enrollment and will receive a single oral dose of CCI of LY3484356 followed 4 hours later by a single dose of CCI of [^{14}C]-LY3484356 (containing CCI of radioactivity [microtracer]).

Participants in both study parts will receive a follow-up phone call approximately 7 days after discharge from the study site.

The study duration for participants in each cohort is expected to be as follows:

- **Part 1:** up to 59 days
- **Part 2:** up to 46 days

Data Monitoring Committee: No


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2. Introduction

LY3484356 is an orally bioavailable, non-covalent, selective estrogen receptor degrader (SERD) in development for the treatment of breast cancer and endometrial cancer (EC). It is a potent degrader and selective antagonist of wild-type and mutant estrogen receptor α (ERα or ESR1).

Full details of the preclinical safety, efficacy, and pharmacokinetics (PK), and clinical PK may be found in the Investigator's Brochure (IB).

2.1. Study Rationale

Study J2J-MC-JZLE (JZLE) is a Phase 1 open-label, 2-part study of LY3484356 containing [^{14}C]-LY3484356 administered to healthy females of nonchildbearing potential.

Part 1 of this study determines the disposition of [^{14}C]LY3484356 and identifies the metabolites present in plasma, urine, and feces following a single oral administration of LY3484356 containing [^{14}C]-LY3484356. This provides understanding of the clearance pathways of LY3484356, which is important to assess the likelihood of effects of renal or hepatic impairment on the disposition of LY3484356 and the likelihood for drug-drug interactions (DDIs) with LY3484356. Furthermore, knowledge of the metabolism and elimination of parent drug and its metabolites and major circulating metabolites is useful for evaluating needs of metabolite(s)-mediated DDI studies and metabolite(s) in safety testing requirements elucidated in the Food and Drug Administration Guidance and International Conference on Harmonisation M3.

Part 2 of this study determines the absolute bioavailability of LY3484356 of a tablet formulation in humans using an intravenous (IV) microtracer of [^{14}C]-LY3484356 (containing CCI radioactivity). Absolute bioavailability information aids quantitative evaluation of drug disposition of LY3484356 and subsequent planning and designing of additional clinical pharmacology studies.

2.2. 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 (Brayet al. 2018). Treatment options for women with breast cancer are largely determined by tumor HR and HER2 status (NCCN 2018; Waks and Winer 2019), and over 2 thirds of breast cancers express estrogen receptor (ER) - a key driver of breast cancer initiation and progression. For patients with advanced HR+/HER2-status, treatment includes endocrine therapy (ET) (e.g., tamoxifen, anastrozole, letrozole, fulvestrant) alone or in combination with cyclin-dependent kinase (CDK)4 and 6 inhibitors as indicated (e.g., abemaciclib, palbociclib, or ribociclib), as well as standard chemotherapy (e.g., capecitabine, docetaxel, paclitaxel, nab-paclitaxel [NCCN 2018; Waks and Winer 2019]). For patients with advanced HR+/HER2+status, treatment includes HER2-directed therapies e.g., trastuzumab, pertuzumab, or trastuzumab emtansine administered alone and in combination with other HER2-directed therapies, chemotherapy, or ET.

In most ER+ breast cancers, ER is an important therapeutic target even after development of resistance to endocrine therapies (Weatherman et al. 1999; Baselgaet al. 2012; Turner et al. 2015; Finn et al. 2016; André et al. 2019). SERDs are one of the treatment options for estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer patients. Fulvestrant is currently the only regulatory agency-approved SERD for the treatment of ER+ metastatic breast cancer (mBC) (Nardone et al. 2019). Its efficacy is highly dose-dependent, where increasing the administered dose led to improved survival (Di Leo et al. 2014). However, the intramuscular (IM) route of fulvestrant administration limits the amount of fulvestrant that can be given to patients. 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 efficiency (Nardone et al. 2019).

Endometrial cancer, while less frequently diagnosed than breast cancer, is increasing worldwide. In the United States, the incidence of EC has increased by approximately 12,000 cases between 2013 and 2019 (Howlader et al. 2020). Endometrioid EC represents about 80% of EC cases, and overexpression of estrogen may contribute to tumor proliferation (Ellenson et al. 2011).

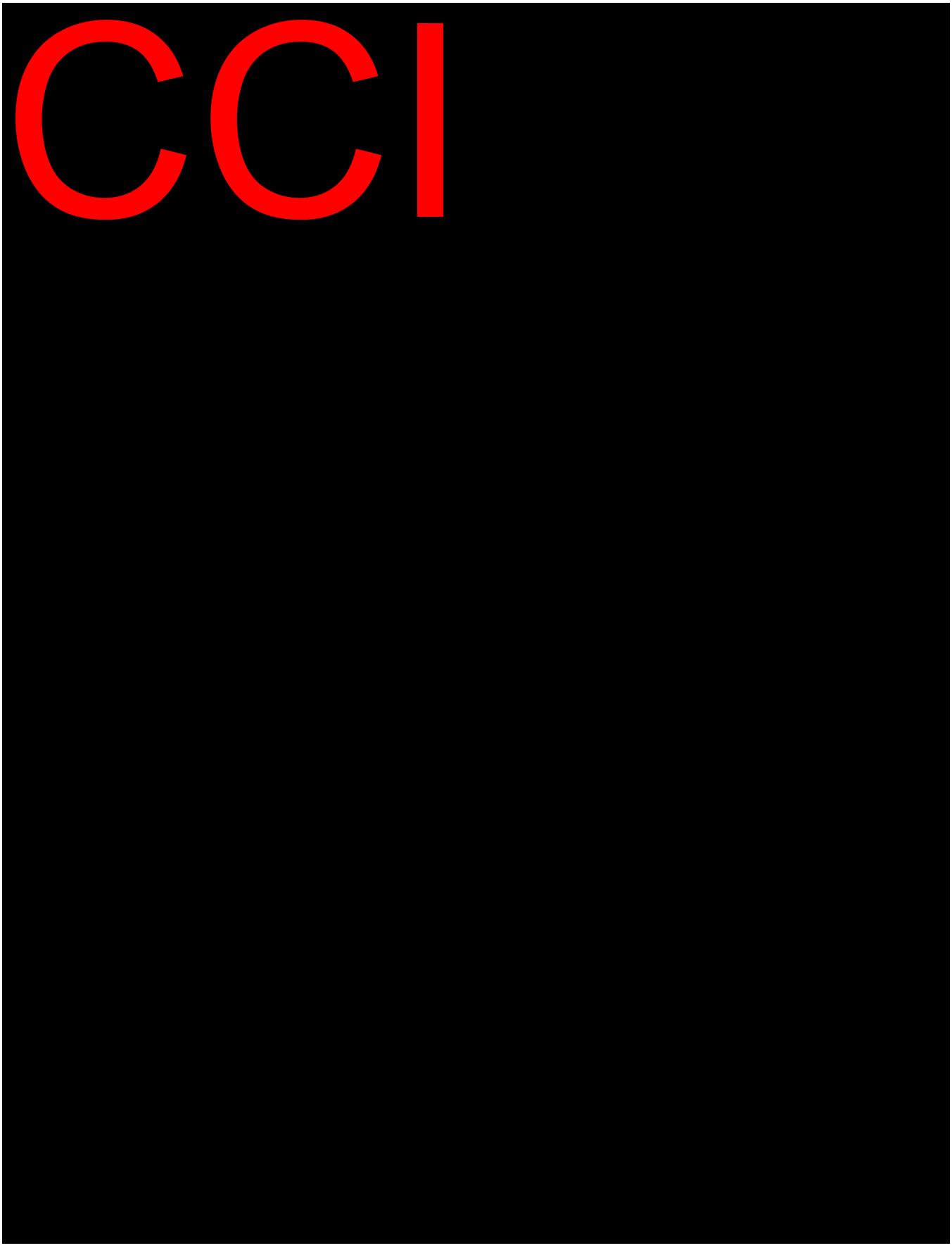
Patients with ER+ breast cancer have several treatment options. However, at the time of progression on ET, the disease becomes less responsive, and options are often limited to chemotherapy. Mutations in ESR1 can lead to an estrogen independent activation of ER pathway, driving tumor growth and resistance to commonly used estrogen deprivation strategies (eg, aromatase inhibitors). Mutant ER α mutant ER+, HER2- breast cancers are potentially amenable to therapy with LY3484356 based on preclinical data. Additionally, for ER+, HER2+ breast cancers, after progression on prior HER2 directed therapies, chemotherapy, and type 1 diabetes mellitus, clinical evidence supports the administration of fulvestrant, a SERD, in combination with trastuzumab (Robertson et al. 2010). The clinical benefit in this patient population could potentially be further improved with the use of LY3484356 as SERD.

2.2.2. Clinical Pharmacokinetics

Pharmacokinetic data from cancer patient studies showed that maximal plasma concentrations were reached approximately 4 hours post dose with an elimination half-life of approximately 25 to 30 hours. Increases in exposures were also observed from 200 to 1200 mg QD in patient studies and were approximately dose proportional. Additional content is described in Section 5.1.1 in the IB.

2.3. Benefit/Risk Assessment

LY3484356 is a potent antagonist and degrader of ERα and has demonstrated significant activity in preclinical models against ER wild-type and mutant tumors. There is no anticipated benefit for the healthy participants in this study.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3. Objectives and Endpoints

Part 1

Objectives	Endpoints
Primary	
• To determine the disposition of radioactivity in healthy nonchildbearing women following oral administration of a single dose of CCI [^{14}C]-LY3484356	• Urinary and fecal excretion of total radioactivity over time expressed as a percentage of the total radioactive dose
Secondary	
• To determine the pharmacokinetics (PK) of total radioactivity and LY3484356 in plasma following a single oral dose of CCI [^{14}C]-LY3484356	• AUC(0-∞) and C_{max} for radioactivity and LY3484356 in plasma
• To assess the mass balance by quantifying radioactivity excretion in urine, feces, and expired air (if applicable)	• Total radioactivity recovered in urine, feces, and expired air (if applicable)
• To identify metabolites of LY3484356 in plasma, urine, and feces	• Total number of metabolites and identification of metabolite
• To assess the safety and tolerability of a single dose of CCI [^{14}C]-LY3484356 CCI in healthy nonchildbearing women	• A summary of TEAEs

Part 2

Objectives	Endpoints
Primary	
• To determine the absolute bioavailability of LY3484356 following a single oral dose of CCI of LY3484356 along with an IV dose of CCI of [^{14}C]-LY3484356 CCI	• absolute bioavailability (F) of LY3484356

Secondary	
• To evaluate the PK of LY3484356, [^{14}C]-LY3484356, and total radioactivity following oral dosing of LY3484356 and IV dosing of [^{14}C]-LY3484356 • To assess the safety and tolerability of LY3484356 following a single oral dose of CCI LY3484356 along with an IV dose of CCI of [^{14}C]-LY3484356 CCI in healthy nonchildbearing women	• AUC(0-∞) and C_{max} for total radioactivity, [^{14}C] LY3484356, and LY3484356 in plasma • A summary of TEAEs

Abbreviations: AUC0-∞ = area under the concentration-time curve from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; F = absolute bioavailability (LY3484356 only); TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study JZLE is an open-label, 2-part, disposition and absolute bioavailability study of [^{14}C]-LY3484356 in healthy females with nonchildbearing potential at a single Phase 1 CRU. In Part 1, it is planned that up to 6 participants may be enrolled to ensure that at least 4 participants complete the study or have evaluable PK data. In Part 2, it is planned that up to 8 participants may be enrolled to ensure that at least 6 participants complete the study or have evaluable PK data for both treatments (oral and IV). Participants in Part 1 will not participate in Part 2, nor will participants in Part 2 participate in Part 1. Part 1 and Part 2 are independent of each other and do not need to be conducted in sequential order.

The schemata in Section 1.2 illustrate the study design.

Safety assessments, including AEs, clinical laboratory tests, vital signs, and ECGs, and blood sampling for PK, will be performed according to the SoA (Section 1.3).

4.1.1. Screening (Part 1 and Part 2)

All participants will be screened within 28 days prior to enrollment.

4.1.2. Treatment and Assessment Period

Part 1:

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, following an overnight fast of at least 10 hours, participants will receive a single oral dose of CCI of [^{14}C]-LY3484356 CCI administered as an oral solution.

Participants will be discharged from the CRU as early as Day 12 and up to Day 22, provided recovery of radioactivity has reached the following threshold values:

- ≥90% of the radioactive dose is recovered, and
- ≤1% of the radioactive dose per day is recovered in excreta (urine and feces combined) for 2 consecutive days on which a fecal sample is collected.

Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the sponsor and investigator (or designee).

For participants experiencing emesis within 4 hours following ^{14}C dosing, vomitus will be collected. Attempts will be made to collect vomitus from participants experiencing emesis after 4 hours post dose. All vomitus will be collected and stored for possible analysis as deemed appropriate.

Part 2:

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, following an overnight fast of at least 10 hours, participants will receive a single oral dose of CCI of LY3484356 as CCI tablets and followed CCI later by a single dose of CCI of [^{14}C]-LY3484356 (containing CCI of radioactivity [microtracer]) administered as approximately a CCI IV infusion. Participants will remain resident in the CRU until Day 9.

During the infusion and for at least 2 hours post-infusion, the blood samples will be taken from the arm contra-lateral to the infusion site.

4.1.3. Follow-up (Part 1 and Part 2)

Participants will receive a follow-up call approximately 7 days after clinic discharge.

4.2. Scientific Rationale for Study Design

This study has an open-label design because the study endpoints are not considered subjective. This study also has no control treatment which is standard and widely used in radiolabeled studies.

In Parts 1 and 2, oral administration has been chosen since this is the intended clinical route of LY3484356 administration.

The IV microtracer method to be used in Part 2 allows for simultaneous oral and IV dosing in the same participants, which is expected to result in less variability in absolute bioavailability estimates as the systemic clearance is equivalent for the IV and oral doses.

Analysis of urine and fecal concentrations of [^{14}C]-LY3484356 and total radioactivity will allow for determination of the amount and percentage of LY3484356 excreted unchanged in urine and feces.

Conducting the study in healthy participants will allow the evaluation of LY3484356 disposition and bioavailability in the absence of concomitant medications and comorbidities. Healthy females of nonchildbearing potential have been selected as the study population since the pharmacologic mechanism of LY3484356 is to degrade the ER, and effects on the female reproductive organs are expected (see Section 2.3).

The doses, participant population, study duration, and sample collection timing are considered adequate to achieve the study objectives.

4.3. Justification for Dose

4.3.1. LY3484356

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4.3.2. Radioactive Dose

For Part 1, the planned radioactive dose of CCI of [^{14}C]-LY3484356 CCI is expected to provide a sufficient radioactive signal to achieve the study objectives with minimal radiation risk to participants.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed all scheduled procedures shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last follow-up phone call for the last participant in the study.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

The nature of any conditions present at the time of the physical examination and any pre-existing conditions will be documented.

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant

2. Participants who are overtly healthy as determined by medical assessment including medical history, physical examination, laboratory tests, 12-lead ECG, and vital signs.
3. Participants who have clinical laboratory test results within the normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
4. Participants who have venous access sufficient to allow for blood sampling as per the protocol.
5. Participants who have a history of a minimum of 1 bowel movement per day (Part 1 only).

Weight

6. Body mass index within the range 18.0 to 35.0 kg/m^2 (inclusive).

Sex

7. Female participants of nonchildbearing potential. This includes females who are not pregnant, non-lactating and either:
   - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy or bilateral salpingectomy, bilateral tubal ligation, or bilateral tubal occlusion), or alternate medical cause/congenital anomaly (e.g., Müllerian agenesis). For individuals with permanent infertility due to an alternate medical cause/congenital anomaly, investigator discretion should be applied to determining study entry.

     or

   - Postmenopausal (see Appendix 4 [Section 10.4] for details)

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. Have known allergies to LY3484356, related compounds or any components of the formulation as appropriate, or history of significant atopy
2. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee)
3. Current or chronic history of liver disease or known hepatic or biliary abnormalities (such as symptomatic gallstones)
4. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee)
5. Have a clinically significant abnormality of blood pressure and/or pulse rate as determined by the investigator
6. Have a history or presence of cardiovascular (e.g., symptomatic bradycardia with resting heart rate of <60 bpm [asymptomatic bradycardia is acceptable]), respiratory, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data. Appendectomy, and hernia repair are considered as acceptable. Gilbert's syndrome with a total bilirubin ≤3.0 × ULN and direct bilirubin within normal limits is acceptable. Cholecystectomy is not acceptable.
7. History of alcoholism or drug/chemical abuse within 2 years prior to check-in
8. Alcohol consumption of > 14 units for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits
9. Positive ethanol urine test result or positive urine drug screen at screening or check-in
10. Show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen
11. Show evidence of hepatitis C and/or positive hepatitis C antibody. Participants with a positive hepatitis C antibody test result can have a confirmatory hepatitis C RNA test.
12. Have evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies
13. Have donated blood of more than 500 mL within the previous 3 months of study screening, have donated plasma from 2 weeks prior to screening, or have donated platelets from 6 weeks prior to screening

Prior/Concomitant Therapy

14. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing, unless deemed acceptable by the investigator (or designee)
15. Use or intend to use any prescription medications/products within 14 days prior to dosing until completion of the follow-up phone call, unless deemed acceptable by the investigator (or designee) and/or sponsor
16. Use or intend to use slow-release medications/products considered to still be active within 14 days or 5 half-lives prior to dosing (whichever is longer), unless deemed acceptable by the investigator (or designee) and/or sponsor
17. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to dosing until completion of the follow-up phone call, unless deemed acceptable by the investigator (or designee) and/or sponsor

Prior/Concurrent Clinical Study Experience

18. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 30 days prior to dosing, or 5 half-lives; whichever is longer
19. Have previously completed or withdrawn from this study or any other study investigating LY3484356, and have previously received LY3484356
20. Have previously received a SERD in the past 30 days prior to dosing, or 5 half-lives; whichever is longer

Other Exclusions

21. Smoke more than 10 cigarettes or use the equivalent tobacco, smoking-cessation products, nicotine-containing products, or e-cigarettes (nicotine and non-nicotine) per day. Participants must be willing to abstain from smoking while resident at the CRU
22. Received or intend to receive a vaccination within 30 days of dosing or while on study
23. Receipt of blood products within 2 months prior to check-in
24. History of a major surgical procedure within 30 days prior to screening
25. have had exposure to significant diagnostic, therapeutic, or employment-related radiation within 12 months prior to dosing (e.g. serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring)
26. Intend to donate ova from check-in (Day -1) and at any time postdose
27. **Part 1 only:** Participation in a radiolabeled drug study where exposures are known to the Investigator (or designee) within the previous 4 months prior to check-in, or participation in a radiolabeled drug study where exposures are not known to the Investigator (or designee) within the previous 6 months prior to check-in. The total 12-month exposure from this study and a maximum of 2 other previous radiolabeled studies within 4 to 12 months prior to this study will be within the Code of Federal Regulations (CFR) recommended levels considered safe, per United States Title 21 CFR 361.1: less than 5000 mrem whole body annual exposure with consideration given to the half-lives of the previous radiolabeled study interventions received.

28. **Part 2 only:** Participation in any other radiolabeled investigational study intervention trial within 12 months prior to check-in. Any previous radiolabeled study intervention must have been received more than 12 months prior to check-in.
29. Participants who, in the opinion of the investigator (or designee), should not participate in this study.

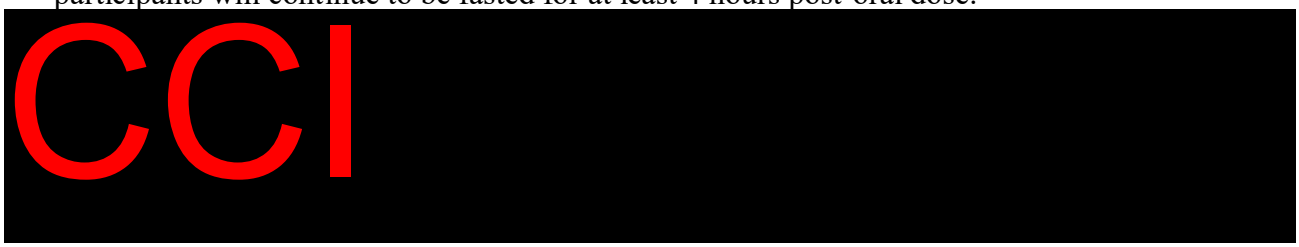
5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

While confined at the CRU, participants will receive a standardized high fiber diet at scheduled times that do not conflict with other study-related activities. Pitted prunes or prune juice may be given on an as-needed basis to aid in normal bowel function and will not be considered a concomitant medication.

Participants will refrain from the consumption of red wine, Seville oranges, Seville orange-containing foods or beverages, poppy seeds, grapefruit or grapefruit juice, from 7 days before check-in until through discharge from the CRU.

In both Parts 1 and 2, oral dosing will be preceded by an overnight fast of at least 10 hours; participants will continue to be fasted for at least 4 hours post-oral dose.



5.3.2. Caffeine, Alcohol, and Tobacco

1. Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 72 hours prior to check-in through discharge from the CRU.
2. During each dosing session, participants will abstain from alcohol for 72 hours prior to check-in through discharge from the CRU.
3. Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the CRU.

5.3.3. Activity

1. Participants will abstain from strenuous exercise from 5 days prior to check-in through discharge from the CRU. Participants may participate in light recreational activities during the study (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened up to 1 time. The interval between re-screenings should be at the discretion of the investigator. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

If participants have minor deviations in screening assessments (e.g., laboratory safety tests, vital signs) these may be repeated at the investigator's discretion to confirm eligibility.

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

Not applicable.

6. Study Intervention

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

6.1. Study Interventions Administered

Part 1:

Study Intervention	[^{14}C]-LY3484356
Dose Formulation	solution
Unit Dose Strength	TBC
Route of Administration	Oral
Sourcing	provided centrally by the sponsor

Part 2:

Study Intervention	[^{14}C]-LY3484356	LY3484356
Dose Formulation	solution	tablet
Unit Dose Strength	TBC	CCI [redacted] LY3484356)
Route of Administration	IV microtracer	oral
Sourcing	provided centrally by the sponsor	provided centrally by the sponsor

6.1.1. Administration Details

In Part 1, participants will receive a single oral dose of CCI of [^{14}C]-LY3484356 CCI [redacted] as an oral solution with a total volume of CCI mL (dose volume + container rinses + water chaser).

In Part 2, participants will receive a single oral dose of CCI LY3484356 as CCI -mg tablets with 240 mL of room temperature water followed 4 hours later by a single dose of CCI [^{14}C]-LY3484356 CCI [redacted] radioactivity [microtracer]) as an IV infusion over CCI [redacted] minutes (±1 minute).

In both parts, an additional 100 mL of water may be administered if needed.

Each unit dose will be prepared by qualified CRU staff. Each unit dose container will be appropriately labeled.

LY3484356 tablets should be swallowed whole. Participants should not break, crush, or chew the study intervention.

All oral doses will be administered while the participants are seated, and participants will not be permitted to lie supine for 4 hours post-oral dose unless clinically indicated or for study procedures. Participants may be asked to be semi-supine/supine for the IV dosing.

On dosing days, participants will adhere to meal restrictions as outlined in Section 5.3.1.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, nonrandomized study.

6.4. Study Intervention Compliance

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

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

6.5. Concomitant Therapy

Participants will refrain from use of any prescription or nonprescription medications/products during the study until the follow-up phone call, unless the investigator (or designee) and/or sponsor have given their prior consent.

A mild laxative (i.e. Milk of Magnesia or Colace) may be used to help with bowel movements, if necessary.

The Clinical Pharmacologist (CP)/CRP should be contacted if there are any questions regarding concomitant or prior therapy. If acetaminophen (or paracetamol) treatment is needed for pain management, the maximal allowed dose will be 3 g/day from all acetaminophen-containing medicinal products. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Lilly CP/CRP, or designee.

6.6. Dose Modification

Dose modification will not be permitted in this study.

6.7. Intervention After the End of the Study

LY3484356 will not be made available to participants after completion of the study.

7. Participant Discontinuation/Withdrawal from the Study

Participants discontinuing from study intervention prematurely for any reason should complete AE and other follow-up/early discontinuation procedures as per the SoA (Section 1.3).

Participants discontinuing from the study prematurely for any reason must complete AE and follow-up/early discontinuation procedures as per the SoA (Section 1.3).

Discontinuation of the study as a whole is described in Appendix 1 (Section 10.1).

7.1. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at her own request
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

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. See SoA (Section 1.3) 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, she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

8.1. Efficacy Assessments

Not applicable to this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Physical examinations and routine medical assessments will be conducted as specified in the SoA (Section 1.3) and as clinically indicated.

8.2.2. Vital Signs

For each participant, supine blood pressure, supine pulse rate, and oral body temperature should be assessed at the times indicated in the SoA (Section 1.3).

Blood pressure and pulse rate should be measured singly after at least 5 minutes supine. For each individual participant, the same cuff size should be used throughout the study for the measurements of blood pressure. The cuff should be attached to the participant's dominant arm, when possible.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Where orthostatic measurements are required, participants should be supine for at least 5minutes and then participants will stand, and standing blood pressure will be measured after 2 minutes, but no longer than 3 minutes. If the participant feels unable to stand, supine vital signs only will be collected. Additional vital signs may be measured if warranted.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake

during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and, ideally, while the participant is still present. This interpretation is to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Assessments

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

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator, CP, or CRP.

- 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 SoA and standard collection requirements.

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

8.2.5. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes including hematology and clinical chemistry

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 2; Section 10.2), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline (Day -1) results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline (except for patients with Gilbert's syndrome)

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 CP/CRP. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (e.g., heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including nonprescription), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN with hepatic signs/symptoms*, or ALT or AST ≥5 × ULN
ALP <1.5 × ULN	ALP ≥3 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline with hepatic signs/symptoms*, or ALT or AST ≥3 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥2 × baseline (except for patients with Gilbert's syndrome)

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time/international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or computed tomography scan).

Based on the participant's history, initial results, and at investigator's discretion, further testing should be considered in consultation with the CP/CRP, including tests for cytomegalovirus, Epstein-Barr virus, acetaminophen levels, urine toxicology screen, Wilson's disease, blood alcohol levels, and urinary ethyl glucuronide. 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, or a liver biopsy.

Additional hepatic data collection (hepatic safety eCRF) in study participants who have abnormal liver tests during the study:

Additional hepatic safety data collection in hepatic safety eCRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5 × ULN on 2 or more consecutive blood tests (if baseline ALT <1.5 × ULN)
   - In participants with baseline ALT ≥1.5 × ULN, the threshold is ALT ≥3 × baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2 × ULN (if baseline TBL <1.5 × ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5 × ULN, the threshold should be TBL ≥2 × baseline
3. Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN)
   - In participants with baseline ALP ≥1.5 × ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

NOTE: the interval between the 2 consecutive blood tests should be at least 2 days.

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

The definitions of the following events can be found in Appendix 3 (Section 10.3):

- AEs
- SAEs
- Product complaints (PCs)

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

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

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2).

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the informed consent form (ICF)	participation in study has ended	as soon as possible upon site awareness	AE eCRF	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	signing of the informed consent form (ICF)	start of intervention	within 24 hours of awareness	SAE Report	SAE paper form
SAE and SAE updates – after start of study intervention	start of intervention	resolution of the SAE	within 24 hours of awareness	SAE Report	SAE paper form
SAE – after participant's study participation has ended **and** the investigator becomes aware	after participant's study participation has ended	N/A	Promptly	SAE Report	N/A
Product Complaints					
PC associated with an SAE or might have led to an SAE	start of study intervention	end of study intervention	within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	start of study intervention	end of study intervention	within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	as soon as possible upon site awareness	originally completed Product Complaint form with all changes signed and dated by the investigator	N/A

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

8.4. Product Acceptability and Palatability Assessments

Participants in Part 1 will be asked to provide responses to questions designed to assess the acceptability and palatability of the solution after treatment administration. The questionnaire will assess the participant's experience relating to the taste, mouthfeel, and aftertaste of the solution in the oral cavity. The questionnaire will be completed by the participant immediately after administration of the solution i.e. within 5 minutes of dosing.

8.5. Treatment of Overdose

For this study, any dose of LY3484356 greater than CCI within a 24-hour time period will be considered an overdose. In the event of an overdose, the investigator or treating physician should:

1. Contact the Lilly CP immediately
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities

In case of overdose, supportive therapy should be used. There is no known antidote to LY3484356 overdose.

8.6. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), in Part 1, venous blood samples of up to CCI each will be collected to determine the plasma concentrations of LY3484356; venous blood samples of up to CCI will be collected to determine the plasma concentrations of total radioactivity; venous blood samples of up to CCI will be collected to determine metabolite profiling of LY3484356 in plasma (as outlined in Appendix 2 [Section 10.2.1]). Plasma from the 1 × CCI blood samples may be used to determine metabolite profiling of LY3484356. In Part 2, at the visits and times specified in the SoA (Section 1.3), venous blood samples of up to CCI each will be collected to determine the plasma concentrations of LY3484356; venous blood samples of up to CCI will be collected to determine the plasma concentrations of [^{14}C]-LY3484356 and to determine the plasma concentrations of total radioactivity. Up to 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded, as well as the date and time of each LY3484356 dose.

In Part 1, urine samples will be collected for the determination of total radioactivity and metabolite profiling (total number and identity). In Part 1, feces samples will be collected for the determination of total radioactivity and metabolite profiling (total number and identity). Urine and feces will be collected before IP administration (control samples); however, the inability to produce a urine or fecal sample will not be considered a protocol deviation. After dosing with IP, cumulative feces and urine samples will be collected in specified containers according to the SoA (Section 1.3) until the specified release criteria have been met.

Urine will be collected at the specified intervals into 1 or more containers (depending on volume excreted) according to the SoA (Section 1.3) until the specified release criteria have been met. An aliquot of each sample will be analyzed to determine concentrations of LY3484356, yield the percentage radioactivity recovered within that interval, and to determine its metabolic profile.

Feces from each bowel movement will be collected and the time of collection will be noted. Fecal samples will be pooled over each 24-hour collection period according to the SoA (Section 1.3) and analyzed to yield the percentage radioactivity recovered over that period as well as to determine its metabolic profile.

8.6.1. Bioanalysis

In Parts 1 and 2, plasma concentrations of LY3484356 will be determined using a validated liquid chromatography with tandem mass spectrometry bioanalytical method CCI [redacted]

In Part 1, total radioactivity will be determined in plasma by CCI [redacted] and in urine and feces by CCI [redacted]. Plasma concentration of [^{14}C]-LY3484356 will be quantified by high performance CCI [redacted] Profiling and identification of metabolites in plasma CCI [redacted], urine, and, where possible, feces will be conducted using standard laboratory procedures CCI [redacted] As needed, plasma profiling and plasma metabolite identification may be done by CCI [redacted]

In Part 2, concentrations of [^{14}C]-LY3484356 in plasma will be determined using CCI [redacted] Concentrations of total radioactivity in plasma will be determined using CCI [redacted] Specifics of the analytical methods will be provided in separate documents.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Samples collected for the analysis of plasma concentrations of LY3484356 may be stored and analyzed for future exploratory analysis, such as quantification of metabolites of LY3484356.

8.6.2. Expired Air Samples

A sample of expired breath will be collected for analysis of $^{14}CO_2$ at the times indicated in the SoA (Section 1.3). If a significant amount of the radioactivity is present in breath samples, the raw data will be extrapolated to provide an estimate of the percentage dose eliminated via $^{14}CO_2$. Additional breath samples may be collected at some or all of the times that blood samples are drawn and only analyzed if needed.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Genetics

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

8.9. Biomarkers

Biomarkers are not evaluated in this study.

8.10. Immunogenicity Assessments

Not applicable for this study.

8.11. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

Not applicable for this study.

9.2. Analyses Sets

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Enrolled/Intent-to-Treat	All participants assigned to treatment, regardless of whether they take any doses of IP, or if they take the correct treatment.
Safety	All enrolled participants who take at least 1 dose of LY3484356 or [^{14}C]-LY3484356, whether or not they completed all protocol requirements.
Pharmacokinetic Analysis	All participants who received at least 1 dose of LY3484356 or [^{14}C]-LY3484356, and have evaluable PK data.

9.2.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

9.2.2. Study Participant Characteristics

The participant's age, sex, and other demographic characteristics will be recorded and summarized.

9.2.3. Treatment Compliance

The date and time of dosing will be recorded and listed.

9.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on data from all participants who received at least 1 dose of LY3484356 or [^{14}C]-LY3484356 and have evaluable PK data.

Safety analyses will be conducted for all enrolled participants who received at least 1 dose of LY3484356 or [^{14}C]-LY3484356, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.3.1. Safety Analyses

9.3.1.1. Clinical Evaluation of Safety

All study intervention and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with study intervention as perceived by the investigator. Adverse events reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational SAEs will be reported.

9.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include clinical laboratory parameters, vital signs, and ECG parameters. Additional analysis will be performed if warranted upon review of the data.

9.3.2. Pharmacokinetic Analyses

9.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for plasma total radioactivity, plasma LY3484356, and plasma [^{14}C]-LY3484356 will be calculated by standard noncompartmental methods. The primary PK parameters for analysis will be: AUC(0-∞) and C_{max}.

Other noncompartmental parameters, such as t_{max}, $t_{1/2}$, apparent total body clearance of drug calculated after extravascular administration (CL/F), apparent volume of distribution during the terminal phase after extravascular administration (Vz/F), and volume of distribution at steady state (Vdss), may be reported as appropriate. In Part 2, the absolute bioavailability (F) of LY3484356 will also be calculated.

The plasma:total radioactivity ratio of LY3484356 will be calculated for each time point. The percent of radiolabeled dose recovered in feces, urine, and expired air will be calculated in Part 1.

The following PK parameters will be determined from urinary concentrations of total radioactivity: amount of drug excreted in urine (Ae), cumulative Ae, percentage of dose excreted in urine (fe), cumulative fe. Renal clearance (CLR) will also be determined for [^{14}C]-LY3484356 only.

The following PK parameters will be determined from fecal concentrations of total radioactivity: amount of drug excreted in feces (Ae_f), cumulative Ae_f, percentage of dose excreted in feces (fe_f), and cumulative fe_f.

9.3.3. Pharmacokinetic Statistical Inference

No formal statistical analyses are planned.

9.3.4. Pharmacodynamic Analyses

Not applicable for this study.

9.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable for this study.

9.4. Interim Analysis

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

9.5. Sample Size Determination

No formal statistical assessment of sample size has been conducted as this study does not have a hypothesis. The sample size chosen for this study is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the study. In Part 1, up to 6 participants may be enrolled to ensure that at least 4 participants complete the study or have evaluable PK data; in Part 2, up to 8 participants may be enrolled to ensure that at least 6 participants complete the study or have evaluable PK data for both treatments (oral and IV). Each participant will participate in either Part 1 or Part 2. In the event of early withdrawal of any participants and/or to ensure the appropriate number of participants complete each part of the study, replacement participants may be enrolled at the discretion of the sponsor.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

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

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

10.1.3. Informed Consent Process

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

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

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that 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 her data to be used as described in the informed consent.

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

The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (e.g., by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.6. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

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

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

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

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

The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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.

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 electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

10.1.9. Publication Policy

In accordance with the sponsor’s publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the local laboratory.

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 the laboratory safety results.

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate (total CO_2)
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Glucose (random)
Platelets	Creatine kinase
	Gamma-glutamyl transferase (GGT)
Differential WBC (% and absolute counts) of	Blood urea nitrogen (BUN)
Neutrophils	Uric acid
Lymphocytes	Direct bilirubin
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
	Alkaline phosphatase (ALP)
Coagulation[c]	Aspartate aminotransferase (AST)
Prothrombin time (PT)	Alanine aminotransferase (ALT)
Activated partial thromboplastin time (aPTT)	Creatinine
International normalized ratio (INR)	
Urinalysis[a]	
Specific gravity	
pH	Ethanol testing[b]
Protein	Urine drug screen[b]
Glucose	Hepatitis B surface antigen[c]
Ketones	Hepatitis B core antibody[c]
Bilirubin	Hepatitis C antibody[c, d]
Urobilinogen	HIV antibody[c]
Blood	FSH [c, e]
Nitrite	

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

[a] Performed by dipstick. A microscopic examination will be run if blood, protein, nitrites or leukocyte esterase is positive.

[b] Urine drug screen and ethanol (urine) level performed at screening and check-in.

[c] Performed at screening only.

[d] Participants with a positive hepatitis C antibody test result can have a confirmatory hepatitis C RNA test.

[e] Postmenopausal women only.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

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

10.3.2. Definition of SAE

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

SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other

outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

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

  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the eCRF page for AE/SAE and the Product Complaint Form for product complaints.

- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

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 in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.3.5. Reporting of SAEs

SAE Reporting via SAE Report

- Facsimile transmission of the SAE Report is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

1. Women in the following categories are not considered WOCBP:

    a. Premenopausal female with 1 of the following:
        - hysterectomy
        - bilateral salpingectomy
        - bilateral oophorectomy
        - bilateral tubal ligation
        - bilateral tubal occlusion

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

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

    b. Postmenopausal female, defined as women with:
        - 12 months of amenorrhea for women >55, with no need for FSH
        - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective ER modulators, or chemotherapy that induced amenorrhea).

Contraception Guidance:

Contraception is not required during this study.

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

See Section 8.2.5.1 for guidance on appropriate test selection.

The liver safety tests will be performed by the local laboratory. A Lilly-designated central laboratory may be used if the local laboratory is unable to perform the tests.

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**[e]
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, international normalized ratio (INR) (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
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 [d]	Anti-actin antibody [b]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:

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

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

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

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

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

[e] To be performed only in the event of increase AST/ALT.

10.6. Appendix 6: Abbreviations

Term	Definition
ALT	alanine aminotransferase
AMS	accelerator mass spectrometry
AST	aspartate aminotransferase
CIOMS	Council for International Organizations of Medical Sciences
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
DMC	data monitoring committee
Device Deficiencies	Equivalent to product complaint
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.
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
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.
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
NIMP	Non-investigational Medicinal Product
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
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
PPS	per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

11. References

André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu YS, Inoue K, Takahashi M, Pápai Z, Longin AS, Mills D, Wilke C, Hirawat S, Juric D, SOLAR-1 Study GROUP. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med. 2019;380(20):1929-1940.

Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in postmenopausal hormonereceptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520-529.

Bray F, Ferlay J, Soerjomatram I, Siefel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375(20):1925-1936.

Nardone A, Weir H, Delpuech O, Brown H, De Angelis C, Cataldo ML, Fu X, Shea MJ, Mitchell T, Veeraraghavan J, Nagi C, Pilling M, Rimawi MF, Trivedi M, Hilsenbeck SG, Chamness GC, Jeselsohn R, Osborne CK, Schiff R. The oral selective oestrogen receptor degrader (SERD) AZD9496 is comparable to fulvestrant in antagonizing ER and circumventing endocrine resistance. *Br J Cancer.* 2019;120(3):331-339.

[NCCN] Gradishar WJ, Anderson BO, Aft R, Balassanian R, Blair SL, Burnstein HJ, Cyr A, Dang C, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz MP, Goldstein LJ, Isakoff SJ, Lyons J, Marcom PK, Mayer IA, McCormick B, Moran MS, O’ Regan RM, Patel SA, Pierce LJ, Reed EC, Schwartzberg LS, Sitapati A, Smith KL, Smith ML, Soliman H, Somlo G, Telli ML, Ward JH, Kumar R, Shead DA. NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 1.2018 - March 2018.

Robertson JFR, Steger GG, Neven P, Barni S, Gieseking F, Nolè F, Pritchard KI, O'Malley FP, Simon SD, Kaufman B, Petruzelka L. Activity of fulvestrant in HER2-overexpressing advanced breast cancer. *Ann Oncol.* 2010;21(6):1246–1253.

Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang Bartlett C, Zhang K, Giorgetti C, Randolph S, Koehler M, Cristofanilli M, PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med. 2015;373(3):209-219.

Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288-300.

Weatherman RV, Fletterick RJ, Scanlan TS. Nuclear-receptor ligands and ligand-binding domains. *Annu Rev Biochem.* 1999;68:559-581.

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