Protocol J2J-MC-JZLD (b)

Evaluation of the Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Child-Bearing Potential

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Approval Date: 06-Oct-2021

Title Page

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Protocol Number: J2J-MC-JZLD

Amendment Number: (b)

Compound: LY3484356

Study Phase: 1

Short Title: Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Childbearing Potential

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	25-June-2021
Amendment (a)	03-September 2021

Amendment (b)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 4.1. Overall Design (Section 4.1.2. Treatment and Assessment Period)	Updated description of Cohort 1 treatment and assessment period to clarify that a crossover design is utilized. Added further descriptions of study design for each cohort for clarity.	Minor changes for clarity.
Section 1.2. Schema (Section 1.2.1. Cohort 1 – Food-Effect)	Updated schema for Cohort 1 to make it clearer that a crossover design is utilized.	Minor changes for clarity.
Section 1.3. Schedule of Activities (Section 1.3.4. Cohort 4 – Carbamazepine DDI)	Updated the comment for clinical laboratory tests to identify Day 9 instead of Day 8.	To correct inconsistency in previous protocol.
6.1. Study Intervention(s) Administered	Removed the brand name 'Tegretol' for carbamazepine dosing.	Tegretol will not be available to the site. Generic carbamazepine will be utilized instead.
5.1. Inclusion Criteria 10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Removed the note describing that WOCBP could change to a contraception method unaffected by carbamazepine, for consistency with updates to Appendix 4. Updated description of acceptable contraception for WOCBP enrolled in Cohort 5. Clarified that only a copper IUD or vasectomy of sexual partner will be considered acceptable highly effective forms of contraception. Levonorgestrel-releasing IUD or depot progestogen-only injection are not considered acceptable forms of contraception.	To provide clarification to the site on the acceptable contraception methods in Cohort 5, as carbamazepine impacts the effectiveness of many standard contraception methods.
5.1. Inclusion Criteria 10.4. Appendix 4: Contraceptive Guidance	Removed bilateral tubal occlusion as an example of surgical sterilization to define female participants of non-childbearing potential. As per Appendix 4, fallopian tube implants (ie, tubal occlusion) were already	To ensure consistency throughout the protocol and adhere to site guidance regarding surgical sterilization methods.

Section # and Name	Description of Change	Brief Rationale
and Collection of Pregnancy Information	defined as a method of highly effective contraception.	
Throughout	Minor editorial and formatting changes	Minor, therefore have not been summarized.

Abbreviations: DDI = drug-drug interaction; IUD = intrauterine device; WOCBP = women of childbearing potential.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: Evaluation of the Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Child-Bearing Potential

Short Title: Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Childbearing Potential

Rationale:

Study J2J-MC-JZLD (JZLD) is a Phase 1 open-label, 5-cohort study of LY3484356 administered to healthy females of non-childbearing potential. The purpose of 4 cohorts of this study is to assess the safety, tolerability and PK of LY3484356 when dosed with and without food, and in the presence of omeprazole, carbamazepine, or itraconazole.

The results of this study will inform dosing restrictions in ongoing patient trials.

In addition, an exploratory and optional 5th cohort is included for the assessment of the PK of midazolam, a known sensitive CYP3A substrate, when dosed with carbamazepine. The results of this cohort will inform dosing regimens for future carbamazepine drug-drug interaction studies.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the effect of food on the pharmacokinetics (PK) of LY3484356 after a low-fat meal in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356
• To assess the effect of a gastric pH change on the PK of LY3484356 after multiple doses of a PPI (omeprazole) in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356
• Assess the effect of coadministration of LY3484356 given as a single dose (drug-drug interaction [DDI] victim) with itraconazole, on the PK of LY3484356 in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356

• Assess the effect of coadministration of LY3484356 given as a single dose (DDI victim) with carbamazepine, on the PK of LY3484356 in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356
Secondary	
• To evaluate the safety and tolerability of single CCI doses of LY3484356 in healthy females of non-childbearing potential	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

Overall Design

Screening

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

Treatment and Assessment Period

Safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, and blood sampling for PK, will be performed for all cohorts.

Cohort 1 – Food-Effect

Cohort 1 will be an open-label, randomized, crossover design evaluating the effect of food on LY3484356. Eligible participants will take place in 2 treatment periods. Participants will be admitted to the clinical research unit (CRU) on Day -1. On Day 1 of Treatment Period 1, participants will be randomized (1:1) to 1 of 2 treatment sequences; fasted/fed or fed/fasted. . All participants will receive (according to the randomization schedule):

- **Day 1 Treatment Period 1:** CCI LY3484356 in the fed or fasted state
- **Day 1 Treatment Period 2:** CCI LY3484356 in the fed or fasted state

There will be a washout period of 4 days between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 5 of Treatment Period 2.

Cohort 2 – PPI-Effect

Cohort 2 will be an open-label, fixed sequence design evaluating the effect of PPI on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

CCI

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 14.

Cohort 3 – Itraconazole Drug-Drug Interaction

Cohort 3 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of itraconazole on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 17.

Cohort 4 – Carbamazepine Drug-Drug Interaction

Cohort 4 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 27.

Cohort 5 (optional) – Carbamazepine Drug-Drug Interaction with Midazolam

Cohort 5 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on midazolam. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

All participants will remain resident in the CRU until discharge on Day 15.

Follow-up

Participants will attend a follow-up visit 7 to 10 days after discharge from the CRU.

Disclosure Statement: This is an open-label 5-cohort study. Cohort 1 is a 2-period, randomized, crossover design evaluating the effect of food on LY3484356. Cohort 2 is a single period, fixed sequence design evaluating the effect of PPI on LY3484356. Cohort 3 is a single period, fixed sequence design evaluating a potential drug-drug interaction of itraconazole on LY3484356. Cohort 4 is a single period, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on LY3484356. Cohort 5 is a single period, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on midazolam. Cohort 1-4 include healthy females of non-childbearing potential (defined as postmenopausal or infertile due to surgical sterilization or alternate medical cause/congenital anomaly). Cohort 5, which does not include exposure to LY3484356 is open to healthy males and non-pregnant and non-lactating females.

Number of Participants:

In Cohorts 1 and 2, approximately 10 participants will be enrolled in each cohort to ensure that at least approximately 8 evaluable participants in each cohort complete the study.

In Cohort 3, approximately 20 participants will be enrolled to ensure that at least approximately 18 evaluable participants in this cohort complete the study.

In Cohort 4, approximately 26 participants will be enrolled to ensure that at least approximately 18 evaluable participants in this cohort complete the study.

In Cohort 5 (optional), approximately 15, participants will be enrolled to ensure that at least approximately 10 evaluable participants in this cohort complete the study.

Intervention Groups and Duration:

Participants in Cohort 1 will participate in 2 treatment periods, and participants in Cohorts 2, 3, 4, and 5 will participate in 1 treatment period. Participants will be screened within 28 days prior to enrollment and will receive CCI [redacted] oral doses of LY3484356 or CCI [redacted] with a follow-up visit 7 to 10 days after discharge from the study site.

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

- Cohort 1 – Food-Effect: 44 to 47 days
- Cohort 2 – PPI-Effect: 49 to 52 days
- Cohort 3 – Itraconazole Drug-Drug Interaction: 52 to 55 days
- Cohort 4 – Carbamazepine Drug-Drug Interaction: 62 to 65 days
- Cohort 5 – Carbamazepine Drug-Drug Interaction with Midazolam (optional): 50 to 53 days

Data Monitoring Committee: No


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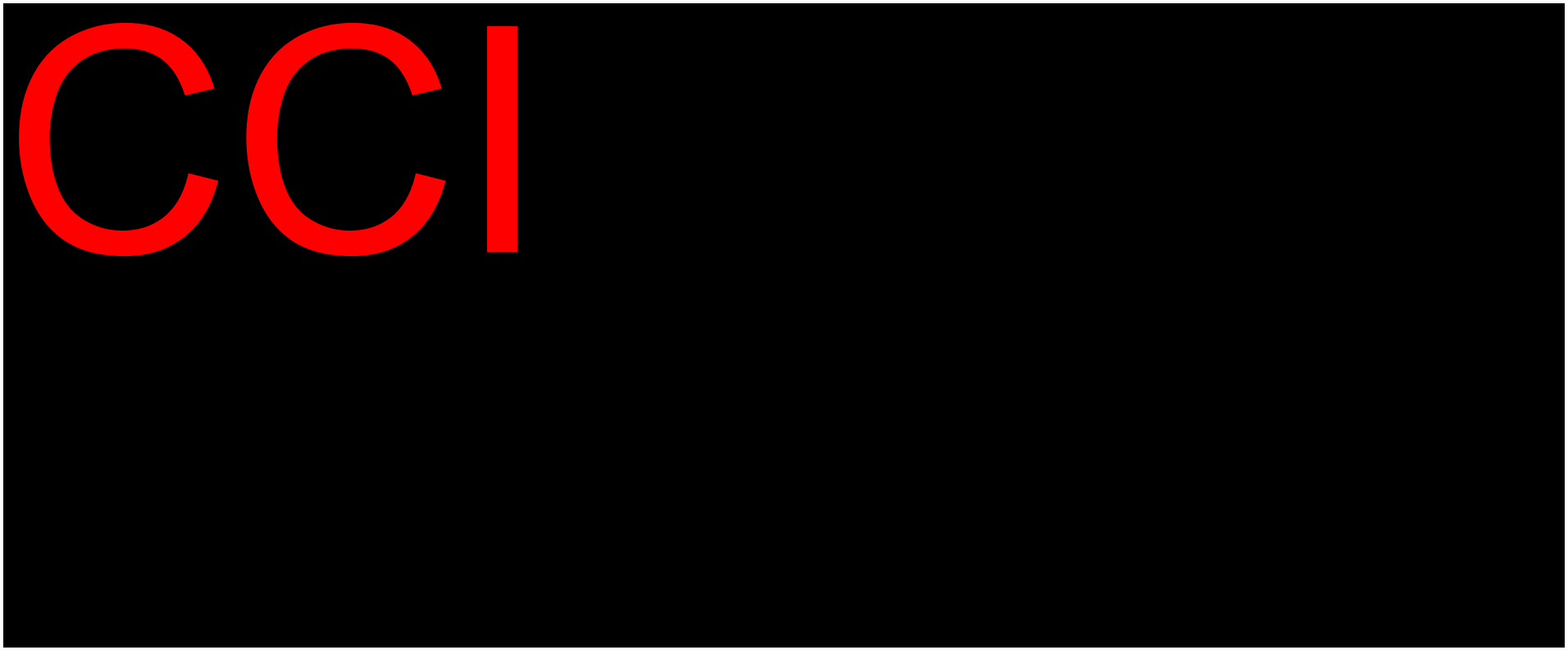
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2. Introduction

LY3484356 is an orally bioavailable, non-covalent, selective estrogen receptor degrader (SERD). 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) may be found in the Investigator's Brochure (IB).

2.1. Study Rationale

Study J2J-MC-JZLD (JZLD) is a Phase 1 open-label, 5-cohort study of LY3484356 administered to healthy females of non-childbearing potential. The purpose of this study is to assess the effect of food on LY3484356, to assess the effect of gastric acid by use of a proton pump inhibitor (PPI; omeprazole) on LY3484356 in the fasted state, and to investigate the effect of the inhibition and induction of CYP3A by use of itraconazole or carbamazepine on LY3484356 in the fasted state. The results of this study will inform dosing instructions in ongoing patient trials.

In addition, an exploratory and optional 5th cohort is included in this study for the assessment of the PK of midazolam, a known sensitive CYP3A substrate, when dosed with carbamazepine. The results of this cohort will inform dosing regimens for future carbamazepine drug-drug interaction 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 (Bray et al. 2018). Clinical decision-making for the management of patients with advanced breast cancer takes into account multiple clinical factors such as hormone receptor-positive (HR)/HER2 status, age, comorbidities, and patient preference. More specifically, treatment options for women with breast cancer are largely determined by tumor HR and HER2 status (NCCN 2018; Waks and Winder 2019).

Over two thirds of breast cancers express estrogen receptor (ER), which is a key driver of breast cancer initiation and progression. Hormone receptor-positive mBC is incurable and therefore considered a serious and life-threatening disease, with a median overall survival of only 2 to 3 years (Cardoso et al. 2012). For patients with advanced HR+/HER2- status, treatment includes endocrine therapy (ET) (eg, tamoxifen, anastrozole, letrozole, fulvestrant) alone or in combination with cyclin-dependent kinase (CDK) 4 and 6 inhibitors as indicated (eg, abemaciclib, palbociclib, or ribociclib), as well as standard chemotherapy (eg, capecitabine, docetaxel, paclitaxel, nab-paclitaxel [NCCN 2018; Waks and Winer 2019]). For patients with

advanced HR+/HER2+ status, treatment includes HER2-directed therapies eg, trastuzumab, pertuzumab, TDM-1 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; Baselga et al. 2012; Turner et al. 2015; Finn et al. 2016; André et al. 2019).

Selective estrogen receptor degraders (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. Even though doses higher than 500 mg per month may lead to better ER degradation, the IM administration route limits the amount of fulvestrant that can be given to patients (Nardone et al. 2019). In addition, several studies have shown that with the current maximum feasible dose, fulvestrant treatment is not able to completely degrade ER in patients and can be associated with early progression (van Kruchten et al. 2015). Thus, there is unmet medical need to develop oral SERDs with higher bioavailability, greater ER targeting, and degradation efficiency (Nardone et al. 2019).

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.

Due to the early stage of the development of LY3484356, the clinical safety profile has not been fully established. There is no previous experience of LY3484356 in healthy participants. LY3484356 has been administered to patients in clinical study J2J-MC-JZLA (JZLA) (200- to 1200-mg QD for 28 days).


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3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of food on the PK of LY3484356 after a low-fat meal in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356
• To assess the effect of a gastric pH change on the PK of LY3484356 after multiple doses of a PPI (omeprazole) in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356
• Assess the effect of coadministration of LY3484356 given as a single dose (DDI victim), with itraconazole, on the PK of LY3484356 in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356
• Assess the effect of coadministration of LY3484356 given as a single dose (DDI victim) with carbamazepine, on the PK of LY3484356 in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, t_{max} of LY3484356
Secondary	
• To evaluate the safety and tolerability of single CCI doses of LY3484356 in healthy females of non-childbearing potential	• Incidence and severity of adverse events (AEs) and SAEs
Exploratory	
• Assess the PK of carbamazepine and carbamazepine 10,11-epoxide • Investigate the impact of coadministration of carbamazepine on the PK of midazolam • Assess exosomal mRNA in plasma	• C_{max} and AUC of carbamazepine and carbamazepine 10,11-epoxide • C_{max} and AUC of midazolam and 1'-hydroxymidazolam with and without carabamazepine. • Exosomal mRNA in plasma

4. Study Design

4.1. Overall Design

Study JZLD is an open-label, 5-cohort, study comprising 4 fixed-sequence crossover cohorts, and 1 randomized (1:1), 2-period crossover cohort. Cohorts 1 to 4 are in healthy females of non-childbearing potential to investigate the safety, tolerability, and PK of LY3484356 when administered as a CCI oral dose, when dosed with and without food, and in the presence of omeprazole, or carbamazepine, and when administered as a CCI oral dose when dosed in the presence of itraconazole. Optional and exploratory Cohort 5 is in healthy participants (males and non-pregnant and non-lactating females) to investigate the PK of the sensitive CYP3A substrate midazolam (and 1'-hydroxymidazolam) when dosed at various times in the presence of carbamazepine.

The schema in Section 1.2 illustrates the study design.

Safety assessments, including AEs, concomitant medications, medical assessments, 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

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

4.1.2. Treatment and Assessment Period

Cohort 1 – Food-Effect

Cohort 1 will be an open-label, randomized, crossover design evaluating the effect of food on LY3484356. Eligible participants will take place in 2 treatment periods. Participants will be admitted to the clinical research unit (CRU) on Day -1. On Day 1 of Treatment Period 1, participants will be randomized (1:1) to 1 of 2 treatment sequences; fasted/fed or fed/fasted. All participants will receive (according to the randomization schedule):

CCI

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 5 of Treatment Period 2.

Cohort 2 – PPI-Effect

Cohort 2 will be an open-label, fixed sequence design evaluating the effect of PPI on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

CCI

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 14.

Cohort 3 – Itraconazole Drug-Drug Interaction

Cohort 3 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of itraconazole on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 17.

Cohort 4 – Carbamazepine Drug-Drug Interaction

Cohort 4 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 27.

Cohort 5 (optional) – Carbamazepine Drug-Drug Interaction with Midazolam

Cohort 5 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on midazolam. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

All participants will remain resident in the CRU until discharge on Day 15.

4.1.3. Follow-up

Participants will attend a follow-up visit 7 to 10 days after discharge from the CRU.

4.2. Scientific Rationale for Study Design

The 2-period, (1:1) randomized crossover design used in Cohort 1 has been chosen as this gives a within-participant assessment as well as effects of period and sequence on the PK of LY3484356 and so increases the power of the study for the given number of participants. The fixed-sequence, crossover design used in Cohorts 2 to 4 of this study is typical for interaction studies where a relatively small number of participants are required, because it allows intraparticipant comparisons and eliminates interparticipant comparisons.

This study will be open-label because the study endpoints are not considered subjective.

Conducting studies in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications, and avoids non-beneficial drug exposures in cancer patients. Healthy females of non-childbearing 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.

In Cohort 2, omeprazole was selected over antacids drugs because the PPI drug class is considered to suppress gastric acid secretion to a greater extent and for a longer duration than some other gastric pH-elevating agents, such as H_2 blockers and antacids.

In Cohort 3, itraconazole has been chosen as the probe drug for Cohort 3 as it is a recommended CYP3A4 inhibitor by the FDA for quantifying clinical victim DDI (Chen et al. 2019).

In Cohorts 4 and 5, carbamazepine has been chosen as the probe drug for Cohorts 4 and 5 as it is an inducer of several cytochrome P450 (CYP) and enzymes responsible for glucuronidation (UGTs). A fixed-sequence design has been selected in these cohorts due to the potential for carryover effects from carbamazepine dosing: the CYP induction caused by carbamazepine can linger for several weeks (Magnusson M et al 2008), which would require an increased study length if a 2-sequence crossover design were selected. In addition, fixed-sequence design is commonly used for DDI studies, and is consistent with FDA guidance.

4.3. Justification for Dose

4.3.1. LY3484356

The clinical safety experience from the JZLA study is described in Section 2.3. LY3484356 was well tolerated at dose levels of 200 mg to 1200 mg once-daily (QD) with no dose-limiting toxicities in Cycle 1. No MTD was established during dose escalation. Given the totality of efficacy, clinical PK, and safety data, the sponsor has selected the 400 mg (QD) dose level to be evaluated in planned patient trials.

The recommended Phase 2 dose of CCI will be used in the food effect and PPI parts of the study (Cohorts 1 and 2). CCI

As described in the IB and Section 2.3, CCI

(Table JZLD.1).

The planned safety monitoring (Section 8.2), clinical tolerability, and favorable nonclinical toxicity profile of LY3484356 support administration of 2 LY3484356 doses (≤ CCI per dose) to healthy females of non-childbearing potential in the present study.

4.3.2. Omeprazole

A dose of CCI omeprazole daily is within the recommended dose as prescribed in the labeling. In addition, multiple doses for 4 consecutive days prior to combination dosing with LY3484356 will ensure maximum inhibition of acid secretion by omeprazole, because the inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after 4 days.

4.3.3. Itraconazole

Itraconazole will be administered as a solution at CCI , then CCI until the administration of LY3484356 on CCI , followed by continued QD administration until CCI This regimen of loading dose, run-in and post-substrate administration is considered optimal to elicit CYP3A4 inhibition.

4.3.4. Carbamazepine

A course of 100 mg BID for 3 days, followed by 200 BID for 3 days and 300 mg BID for 12 days carbamazepine has been selected based on recommendations from the FDA and previous reported doses used to investigate drug-drug interactions with carbamazepine.

Participants will continue dosing with carbamazepine following LY3484356 administration on Day 18 in order to maintain enzyme induction until the PK sampling period is completed. The planned dose levels are within the limits of the recommended therapeutic dose range to treat patients with various medical conditions.

Significant adverse reactions reported with carbamazepine include serious dermatological reactions, strongly associated with HLA-B*1502 and HLA-A*3101 alleles more common in East Asian populations; aplastic anemia and agranulocytosis; hypersensitivity reactions, including drug reactions with eosinophilia and systemic symptoms (DRESS), anaphylactic reactions and angioedema; and suicidal behavior and ideation. The majority of these severe reactions are rarely reported.

Particularly at the start of treatment, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. central nervous system adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia), gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions. The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction.

In DDI studies in which carbamazepine was administrated to healthy participants for less than 1 month in duration, carbamazepine was found to be tolerated with appropriate safety monitoring (Sitsen et al. 2001).

4.3.5. Midazolam

Midazolam is a sensitive CYP3A4 substrate recommended by the FDA for quantifying clinical perpetrator DDI. A CCI oral dose of midazolam is mildly sedating and high enough to ensure that midazolam concentrations remain above the detection limit of the assay CCI to characterize the CYP3A4 induction potential of carbamazepine. A CCI dose of midazolam is a dose considered safe to administer and has been used in previous clinical studies.

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 visit of the last participant in the study.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG. All participants will be women of non-childbearing potential.

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, 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.

Weight

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

For Cohorts 1-4 Sex

6. Female participants of non-childbearing potential. This includes females who are not pregnant, non-lactating and either:
   - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy or bilateral salpingectomy, or bilateral tubal ligation), or alternate medical cause/congenital anomaly (for example, Müllerian agenesis)
     or
   - Postmenopausal as defined in Appendix 4 (Section 10.4)

For Cohort 5 Sex

In addition to Cohort 1-4 sex criteria, Cohort 5 may also include male participants and non-pregnant and non-lactating female participants of childbearing potential.

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

Reproductive definitions and contraceptive requirements are provided in Appendix 4 (Section 10.4).

Informed Consent

7. 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, omeprazole, itraconazole, midazolam, or carbamazepine, 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
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 (eg, symptomatic bradycardia with resting heart rate of <60 beats per minute), 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, hernia repair, and cholecystectomy are considered as acceptable
7. History of alcoholism or drug/chemical abuse within 2 years prior to check-in
8. Alcohol consumption of > 14 units for females and > 21 units in males. 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 breath/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.
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 2 months of study screening

14. Have any medical conditions, medical history, or are taking any medications which are contraindicated in the omeprazole, itraconazole, midazolam, or carbamazepine labels, as appropriate

Prior/Concomitant Therapy

15. 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)
16. Use or intend to use any prescription medications/products within 14 days prior to dosing until completion of the follow-up visit, unless deemed acceptable by the investigator (or designee).
17. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to check-in, unless deemed acceptable by the investigator (or designee)
18. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in until completion of the follow-up visit, unless deemed acceptable by the investigator (or designee)
19. Use or intend to use medications that inhibit or induce CYP3A4 within 14 days prior to dosing until completion of the follow-up visit.

Prior/Concurrent Clinical Study Experience

20. 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
21. Have previously completed or withdrawn from this study or any other study investigating LY3484356, and have previously received LY3484356
22. Have previously received a SERD in the past 30 days prior to dosing, or 5 half-lives; whichever is longer

Other Exclusions

23. 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 whilst resident at the CRU.
24. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.
25. Receipt of blood products within 2 months prior to check-in.
26. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
27. Participants who, in the opinion of the investigator (or designee), should not participate in this study.

In addition, for Cohort 3 only:

28. Have impaired hearing or a history of hearing problems (rationale: because itraconazole has been associated with transient or permanent hearing loss).

In addition, for Cohorts 4 and 5 only (due to carbamazepine administration):

29. Participants of Asian descent.
30. Have history of serious dermatological adverse reaction, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, DRESS; or history of other significant allergic drug reaction, such as anaphylaxis or angioedema.
31. Have laboratory evidence of clinically significant anemia, leukopenia, or hepatic dysfunction; or hyponatremia.
32. History of significant neurological or psychological illness.
33. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
34. Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia Suicide Severity Rating Scale (C-SSRS) or have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, and the ideation or behavior occurred within the past month.

In addition, for Cohort 5 females only (due to carbamazepine administration):

35. Use or intend to use any oral contraceptive drugs containing estrogen and/or progesterone within 30 days prior to dosing

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

During the confinement period, participants will consume only food and beverages that are provided to them by the CRU staff. Standard meals (e.g., breakfast, lunch, dinner, and snack) will be provided to the participants while resident at the CRU.

LY3484356 will be dosed in the fasted state with the exception of in the fed period of Cohort 1.

On fasted dosing occasions, the participants will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, participants may consume water ad libitum.

When participants are dosed in the fed state, they will consume a low-fat breakfast 30 minutes prior to administration of study intervention and participants should eat this meal in 30 minutes or less. No additional food should be allowed for at least 4 hours after drug administration. An example of the low-fat breakfast to be provided is as follows:

	PRO	FAT	CHO	Calories
1c Special K Berry	2.0	0.0	27.0	116.0
4oz Fruit Cup (no citrus)	0.0	0.0	19.0	76.0
1 Slice Toast White Bread	3.0	0.5	12.0	64.5
1 oz Jelly (1 Tbsp)	0.0	0.0	13.0	52.0
1 hard-boiled egg	6.3	5.3	0.6	77
8oz 1% Milk	8.0	1.0	12.0	89.0
Totals	13.0	1.5	113.0	517.5
Total Calories	**52**	**13.5**	**452**	
% of Calories	10%	3%	87%	

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until follow-up. In addition, all other citrus fruits and tomato-based products will not be allowed from the time of check-in until discharge from the CRU.

5.3.2. Caffeine, Alcohol, and Tobacco

1. During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.
2. During each dosing session, participants will abstain from alcohol for 24 hours before the check-in until after collection of the final PK sample.
3. Participants are required to refrain from use of tobacco, smoking-cessation products, nicotine containing products, and e-cigarettes (nicotine and non-nicotine) from check-in and through discharge from the CRU

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.3.4. Other

CCI [redacted]

CCI

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 least 1 week. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

If subjects 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.

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 Intervention(s) Administered

Table JZLD.2. Study Interventions Administered

Study Intervention	LY3484356 (Cohorts 1, 2, and 4)	LY3484356 (Cohort 3)	Omeprazole (Cohort 2)	Itraconazole (Cohort 3)	Carbamazepine (Cohorts 4 and 5)	Midazolam (Cohort 5)
Dosage Formulation	Tablet	Tablet	Capsule	Solution	Tablet	Syrup
Unit dose strength(s)/ Dosage Level(s)	CCI					
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral
Dosing Instructions	CCI					
Sourcing	CCI					

Abbreviation: TP = treatment period

6.1.1. Administration Details

All doses of LY3484356 will administered with approximately 240 mL of room temperature water while in a sitting position.

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

Participants will not be allowed to lie supine for 2 hours after each dosing occasion, unless clinically indicated or for study procedures.

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

Cohort 1 – Food-Effect

A single oral dose of LY3484356 CCI will be administered in the morning of Day 1 in each treatment period.

Cohort 2 – PPI-Effect

A single oral dose of LY3484356 CCI will be administered in the morning of CCI Single oral doses of omeprazole CCI will be administered alone on CCI and in combination with LY3484356 CCI on Day CCI All doses of omeprazole will be administered with approximately 240 mL of room temperature water while in a sitting position. No additional water is required when omeprazole is dosed in combination with LY3484356.

Omeprazole capsules should be swallowed whole. Participants should not break, crush, chew, or empty the contents of the study intervention.

Cohort 3 – Itraconazole Drug-Drug Interaction

A single oral dose of LY3484356 CCI will be administered in the morning of Days CCI Single oral doses of itraconazole CCI will be administered alone on Days CCI No additional water is required when dosing with itraconazole alone.

Cohorts 4 and 5 – Carbamazepine Drug-Drug Interaction

In Cohort 4, a single oral dose of LY3484356 CCI will be administered in the morning of Days CCI Twice-daily oral doses of carbamazepine will be administered alone as CCI Carbamazepine will be administered with LY3484356 on the morning of Day CCI

In Cohort 5, a single oral dose of midazolam CCI will be administered in the morning of Days CCI Twice-daily oral doses of carbamazepine will be administered alone as CCI on Days CCI doses on Days CCI and CCI doses on Days CCI Carbamazepine will be administered with midazolam on the morning of Days CCI

Participants will not be allowed to lie supine for 2 hours after dosing carbamazepine, unless clinically indicated or for study procedure.

On days of LY3484356 or midazolam administration, LY3484356 or midazolam will be given after an overnight fast of at least 10 hours. Subjects will abstain from water 1 hour before and

after dosing (except for water given with the dose). Subjects will remain fasting for at least 2 hours postdose at which time a meal may be served.

Carbamazepine should be taken with breakfast and dinner with approximately 240 mL of room temperature water. The doses should be taken at approximately the same time of day for a given subject. On the days of LY3484356 or midazolam and carbamazepine coadministration, LY3484356 or midazolam should be administered fasted, carbamazepine will then be dosed with breakfast at least 2 hours after LY3484356 or midazolam dosing.

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 study.

In Cohort 1, participants will be assigned a unique number (randomization number) on Day 1. The randomization number encodes the participant's assignment to be dosed in the fed or fasted state on Day 1 of Treatment Period 1 according to the randomization schedule generated prior to the study by the Statistics Department at Covance.

Cohorts 2 to 5 will not be randomized.

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 case report form (CRF).

6.5. Concomitant Therapy

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

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency for concomitant therapy of special interest

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. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will not remain in the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Discontinuation of investigational product (IP) should be considered by the investigator if any of the following occur in a participant:

- an AE that is considered to be intolerable,
- an abnormal safety laboratory test result, determined to be clinically significant by the investigator

In addition, for Cohorts 4 and 5 only:

- systemic hypersensitivity reaction (including signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN), or clinically significant rash
- answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
- answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

7.1.1. Liver Enzymes and Other Laboratory Tests

Discontinuation of the study intervention for abnormal liver tests **should occur** when a participant meets 1 of the following conditions after consultation with the Lilly-designated CP/CRP:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× upper limit of normal (ULN)
- ALT or AST >3× ULN and total bilirubin level (TBL) >2× ULN or international normalized ratio >1.5
- ALT or AST >3× ULN and the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3× ULN
- ALP >2.5× ULN and TBL >2× ULN

- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Appendix 5 (Section 10.5).

Discontinuation of the IP due to abnormal laboratory results **should be considered** by the investigator when a participant meets 1 of the following conditions after consultation with the CP/CRP:

- creatine kinase elevation of >8× ULN (or >1600 IU/L)
- lipase and/or amylase ≥3× ULN (Section 10.5; should be considered by the investigator).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at her own request
- at the request of her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- 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
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the Lilly CP agree it is medically appropriate

to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. Safety follow-up should be performed as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (AEs and SAEs) of the protocol.

7.3. Lost to Follow-up

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

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 5 minutes 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, 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. Suicidal Ideation and Behavior Risk Monitoring

Carbamazepine is considered to be a central nervous system active drug.

Participants being treated with carbamazepine should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

8.2.5.1. C-SSRS

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group (Treatment of Adolescent Suicide Attempters) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. Safety Monitoring

8.2.6. 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 chemistry

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

8.2.6.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix2; 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 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 (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), 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 (for example, ultrasound or computed tomography scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the CP/CRP, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, 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 drug 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 7.3).

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
Serious Adverse Event					

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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 paper form	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 paper form	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 paper form	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. Treatment of Overdose

For this study, any dose of LY3484356 greater than 400 mg 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.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples of up to 2 mL each will be collected to determine the plasma concentrations of LY3484356. In Cohort 3, blood samples of approximately 2 mL will be collected for measurement of concentrations of itraconazole and its metabolite hydroxy itraconazole. In Cohort 4, blood samples of 2 mL will be collected for measurement of concentrations of carbamazepine and carbamazepine 10,11-epoxide at the timepoints specified in the SoA (Section 1.3). In Cohort 5, blood samples of 2 mL will be collected for measurement of concentrations of carbamazepine and carbamazepine 10,11-epoxide and blood samples of 2 mL will be collected for measurement of concentrations of midazolam and 1'hydroxymidazolam at the timepoints specified in the SoA (Section 1.3). 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.

8.5.1. Bioanalysis

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

Concentrations of LY3484356 will be assayed using a validated liquid chromatography mass spectrometry method. 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.

Plasma concentrations of itraconazole, hydroxyitraconazole, carbamazepine, carbamazepine 10,11-epoxide, midazolam, and 1'hydroxymidazolam will be determined using a validated analytical procedure.

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

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

8.8. Biomarkers

In Cohorts 4 and 5, blood samples (10 mL) will be collected for exosomal mRNA analysis as specified in the SoA (Section 1.3). The mRNA of proteins involved in drug disposition will be quantified.

8.9. Immunogenicity Assessments

Not applicable for this study.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary endpoints will be evaluated to assess the potential effect of food on LY3484356, any potential effect of a gastric pH change on the PK of LY3484356, and any potential drug-drug interaction between LY3484356 and itraconazole or carbamazepine.

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 participants who take at least 1 dose of IP.
Pharmacokinetic Analysis	All participants who received at least 1 dose of IP and have evaluable PK.

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 IP and have evaluable PK.

Safety analyses will be conducted for all enrolled participants who received at least 1 dose of IP, 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 IP 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 IP 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 safety 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. PK Parameter Estimation

Pharmacokinetic parameter estimates will be calculated by standard noncompartmental methods. The primary PK parameters for analysis of LY3484356 will be: C_{max}, AUC(0-∞), and t_{max}. Other noncompartmental parameters, such as $t_{1/2}$, apparent total body clearance of drug calculated after extravascular administration, and apparent volume of distribution during the terminal phase after extravascular administration, may be reported as appropriate. Plasma concentrations of itraconazole, carbamazepine, and midazolam, and their metabolites in Cohorts 3, 4, and 5 will be summarized using standard descriptive statistics as appropriate.

9.3.2.2. PK Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate food effect and drug-drug interactions (with omeprazole, itraconazole, or carbamazepine) for LY3484356. Log-transformed C_{max} and AUC(0-∞) parameters for LY3484356 will be evaluated separately. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

To estimate the food effect in Cohort 1, a linear mixed-effects model with period and treatment as a fixed effect and participant as a random effect will be used.

To estimate the effect of a gastric pH change in Cohort 2, and the following drug-drug interactions:

- LY3484356 with itraconazole (Cohort 3)
- LY3484356 with carbamazepine (Cohort 4)
- Midazolam with carbamazepine (Cohort 5),

log-transformed C_{max} and AUC(0-∞) parameters for LY3484356 (Cohorts 2, 3, and 4) and midazolam (Cohort 5) will be analyzed using a linear mixed-effects model with a fixed effect for treatment and a random effect for participant.

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the difference between observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

Pharmacokinetic parameters will be summarized using descriptive statistics.

9.3.3. Pharmacodynamic Analyses

Not applicable for this study.

9.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable for this study.

9.4. Interim Analysis

An interim analysis of safety will be conducted after the completion of Cohorts 1 and 2. The interim analysis will be conducted to inform dosing restrictions in patient trials.

9.5. Sample Size Determination

In Cohorts 1 and 2, approximately 10 participants will be enrolled in each cohort to ensure that at least approximately 8 evaluable participants in each cohort complete the study. The sample size (N=8) will provide at least 80% power that the 90% CI of the ratio is included in the acceptance interval between 0.7 and 1.43, assuming that the expected geometric mean ratio is 1 and CCI [redacted]

In Cohort 3, approximately 20 participants will be enrolled to ensure that at least approximately 18 evaluable participants complete the study. In Cohort 4, approximately 26 participants will be enrolled to ensure that at least approximately 18 evaluable participants in this cohort complete the study. The sample size (N=18) will provide at least 80% power that the 90% CI of the ratio is included in the acceptance interval between 0.8 and 1.25, assuming that the expected geometric mean ratio is 1 and CCI [redacted]

In Cohort 5 (optional), approximately 15, participants will be enrolled to ensure that at least approximately 10 evaluable participants in this cohort complete the study.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/Independent Ethics Committees (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- 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 her representative will explain the nature of the study, including the risks and benefits, to the participant or her legally authorized representative 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, 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 (for example, 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 electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

- 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 (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement 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
Platelets	Creatine kinase
	Gamma-glutamyl transferase
Coagulation	Blood urea nitrogen (BUN)
Prothrombin time (PT)	Direct bilirubin
	Uric acid
Activated partial thromboplastin time (aPTT)	Total protein
International normalized ratio (INR)	Albumin
	Total bilirubin
Differential WBC (absolute counts) of	Alkaline phosphatase (ALP)
Neutrophils	Aspartate aminotransferase (AST)
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Creatinine
Eosinophils	Lipase
Basophils	Amylase
Urinalysis	
Specific gravity	
pH	
Protein	
Glucose	Ethanol testing[a]
Ketones	Urine drug screen[a]
Bilirubin	Hepatitis B surface antigen[b]
Urobilinogen	Hepatitis B core antibody[b]
Blood	Hepatitis C antibody[b]
Nitrite	HIV antibodies[b]
	FSH (if applicable)[b]
	Pregnancy test (if applicable)[c]

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

[a] Performed at screening and check-in only.

[b] Performed at screening only.

[c] Performed in serum on Day -1 and in urine at all other times.

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 (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New 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. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of 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 (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a 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 (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations:

- Medical or scientific judgment should be exercised 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 PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

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

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the (e)CRF page for AE/SAE and the Product Complaint Form for PCs.
- 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 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 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.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF 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 CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in 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)/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 Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

Females are considered a woman of childbearing potential if

- they have had at least one cycle of menses, or
- they have Tanner 4 breast development.

Any amount of spotting should be considered menarche.

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

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

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

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

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

    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 for Cohorts 1-4:

Contraception is not required for these cohorts.

Contraception Guidance for Cohort 5:

Females

All females must have a negative urine pregnancy test result at screening followed by a negative serum result within 24 hours prior to treatment exposure.

Women not of Childbearing Potential

Women not of childbearing potential are not required to use contraception.

Women of Childbearing Potential

Women of childbearing potential who are completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Must…	**Must not…**
agree to either remain abstinent, or stay in a same sex relationship without sexual relationships with males	• use periodic abstinence methods o calendar o ovulation o symptothermal, or o post-ovulation • declare abstinence just for the duration of a trial, or • use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle must agree to use 1 of the following forms of highly effective contraception for the duration of the study and for 28 days after discontinuation of carbamazepine:

- copper intrauterine device (IUD)
- vasectomy of sexual partner.

No other forms of highly effective contraception or effective contraception will be acceptable.

Males

All males should refrain from sperm donation for the duration of the study and for 95 days after the last dose of carbamazepine.

Males in exclusively same sex relationships, as their preferred and usual lifestyle are not required to use contraception.

Males with partners of childbearing potential either must remain abstinent (if this is their preferred and usual lifestyle) or must use condoms during intercourse for the duration of the study and for 95 days following discharge from the study and agree to use an additional highly effective or effective form of contraception.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective. Use of male and female condoms as a double barrier method is not considered effective.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal, • post coital douche • lactational amenorrhea

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

See Section 8.2.6.1 for guidance on appropriate test selection.

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

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

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

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, 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)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]

HBV DNA [d]	Anti-actin antibody [b]
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
AST	aspartate aminotransferase
BID	twice daily
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.
C-SSRS	Columbia Suicide-Severity Rating Scale
DMC	data monitoring committee
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.
IWRS	interactive web-response system
NIMP	Non-investigational Medicinal Product
NOAEL	no observed adverse effect level
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.
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.
SIB	suicidal ideation and behavior
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.

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