Protocol: J2J-MC-JZLK (a)

The Effect of Repeat Dosing of Imlunestrant on CYP3A Activity in Healthy Women of Non-childbearing Potential

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Approval Date: 08-Sep-2022

Title Page

Protocol Title:

The Effect of Repeat Dosing of Imlunestrant on CYP3A Activity in Healthy Women of Non-childbearing Potential

Protocol Number: J2J-MC-JZLK

Amendment Number: (a)

Compound: imlunestrant

Brief Title: imlunestrant and CYP3A activity

Study Phase: 1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana 46285, USA

Regulatory Agency Identifier Number

IND: 145311

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

Document ID: VV-CLIN-074156

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*07-Jun-2022*

Overall Rationale for the Amendment:

Protocol J2J-MC-JZLK has been amended for the purposes of clarification and to align with current clinical practices. The new protocol is indicated by amendment (a) and will be used to conduct study in place of any preceding version of the protocol. The overall changes and rationale for the changes made to the protocol are described in the following table. Note that minor edits have been made throughout the protocol, which are not captured in the amendment summary table.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	It was clarified which assessments were conducted at both the screening visit and Day -1 or the screening visit only.	Updated to be consistent with other sections of the protocol.
1.3 Schedule of Activities (SoA)	The laboratory assessments notes column was updated to state that labs were to be) ○) ○))●) ○ ○) were sent home.	The laboratory results would not be available to check prior to discharge of participants.
5. Study Population	It was clarified that enrollment would be based upon screening results, unless otherwise stated in the inclusion and exclusion criteria.	Updated to align with inclusion and exclusion criteria that were required to be confirmed at check-in or prior to dosing.
5.2 Exclusion Criteria	Exclusion criterion 19 was removed.	Exclusion criterion 19 duplicated the requirements for donation of blood already outlined in in exclusion criterion 32.
5.2 Exclusion Criteria	Exclusion criterion 16 was updated to remove reflex polymerase chain reaction testing for hepatitis B. Reflex polymerase chain reaction testing for hepatitis C was	The polymerase chain reaction test is not available for hepatitis B.

Section # and Name	Description of Change	Brief Rationale
	moved to exclusion criterion 17.	
8.2.3 Electrocardiograms	The requirement for the investigator to document their review of the electrocardiogram printed at the time of collection was removed.	This documentation is not required and was erroneously included.
Appendix 2: Clinical Laboratory Tests	The requirement))) white blood cells was removed ○) 2) ○)○ E	Absolute and % white blood cells only were sufficient.
Appendix 2: Clinical Laboratory Tests	j) ○) ○)○)) remove that urine drug screen would be performed on Day 8.	Updated to be consistent with Schedule of Activities.
Appendix 2: Clinical Laboratory Tests	j)) ○))) hepatitis B surface antigen.	The polymerase chain reaction test is not available for hepatitis B.
Appendix 2: Clinical Laboratory Tests	White blood cell esterase was added to the list of urinalysis parameters.	This will be analyzed as part of the standard urine dipstick.
Appendix 4: Contraceptive and Barrier Guidance	Bilateral tubal occlusion was removed as an example of surgical sterilization.	Bilateral tubal occlusion is not an acceptable form of sterilization.
Appendix 4: Contraceptive and Barrier Guidance	x)) q ○) ○)) partners who become pregn○) has been removed.	Males were not enrolled in this study.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: The Effect of Repeat Dosing of Imlunestrant on CYP3A Activity Healthy Women of Non-childbearing Potential

Brief Title: imlunestrant and CYP3A activity

Rationale:

Study J2J-MC-JZLK (JZLK) is a Phase 1 open-label study of imlunestrant administered to healthy women of non-childbearing potential. The purpose of this study is to assess the effect of imlunestrant on the PK of midazolam, a known sensitive CYP3A substrate.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the effect of multiple doses of imlunestrant on the PK of midazolam (CYP3A4 substrate) in healthy women of non-childbearing potential.	AUC(0-∞) and C_{max} of midazolam when administered alone and in the presence of imlunestrant.
Secondary	
• To evaluate the effect of multiple doses of imlunestrant on the PK of 1'-hydroxymidazolam (a metabolite of midazolam) in healthy women of non-childbearing potential. • To evaluate the safety and tolerability of CCI in healthy women of non-childbearing potential. • Evaluate the PK of imlunestrant in healthy women of non-childbearing potential.	• AUC(0-∞) and C_{max} of 1'-hydroxymidazolam when midazolam is administered alone and in the presence of imlunestrant. • Incidence and severity of AEs and SAEs. • AUC(0-24)$_{,ss}$ and $C_{max,ss}$ of imlunestrant.

Overall Design

Brief Summary:

Study JZLK is an open-label, fixed sequence, crossover study to investigate the effect of imlunestrant on the PK of midazolam and its metabolite 1'-hydroxymidazolam in healthy women of non-childbearing potential. Additionally, the PK, safety, and tolerability of imlunestrant will also be evaluated.

Safety assessments, including AEs, concomitant medications, physical examination, clinical laboratory tests, vital signs, and electrocardiograms, and blood sampling for PK, will be performed.

Number of Participants:

Approximately 20 participants will be enrolled to achieve at least 18 completers to study intervention.

Intervention Groups and Duration:

Screening

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

Treatment and Assessment Period

Participants will be admitted to the CRU on Day -1 (check-in) and will remain resident until Day 11. With regards to dosing, participants will be dosed as follows:

CCI

There will be a washout period CCI between doses of midazolam.

Follow-up

Participants will attend a follow-up visit 5 to 7 days post final dose.

Data Monitoring Committee: No


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2. Introduction

Imlunestrant (LY3484356) is an orally bioavailable, non-covalent, SERD. It is a potent degrader and selective antagonist of wild-)○) ○)i v))i ww I Ex)))intended for oncology indications (breast cancer and EC), in patients where the disease has become less responsive to endocrine therapy, and options are often limited to chemotherapy.

Full details of the preclinical safety, efficacy, and PK may be found in the IB.

2.1. Study Rationale

Study J2J-MC-JZLK (JZLK) is a Phase 1 open-label study of imlunestrant administered to healthy women of non-childbearing potential. The purpose of this study is to assess the effect of imlunestrant on the PK of midazolam, a known sensitive CYP3A substrate.

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 HR/HER2 status, age, comorbidities, and patient preference. More specifically, treatment options for women with breast cancer are largely determined by tumor HR/HER2 status (NCCN 2018; Waks and Winer 2019).

Over two thirds of breast cancers express ER, which is a key driver of breast cancer initiation and progression. HR+ metastatic breast cancer 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 (for example, tamoxifen, anastrozole, letrozole, fulvestrant) alone or in combination cyclin-dependent kinase (CDK)4 and CDK6 inhibitors as indicated (for example, abemaciclib, palbociclib, or ribociclib), as well as standard chemotherapy (for example, capecitabine, docetaxel, paclitaxel, and nab-paclitaxel [NCCN 2018; Waks and Winer 2019]). For patients with advanced HR+/HER2+ status, treatment includes HER2-directed therapies (for example, trastuzumab, pertuzumab, TDM-1 administered alone and in combination with other HER2-directed therapies, chemotherapy, or endocrine therapy).

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).

SERDs are one of the treatment options for ER+/ HER2- breast cancer patients. Fulvestrant is currently the only regulatory agency-approved SERD for the treatment of ER+ metastatic breast cancer (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 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 intramuscular 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).

EC, while less frequently diagnosed than breast cancer, is increasing worldwide. In the United States, the incidence of EC has increased by approximately 12,000 cases between 2013 and 2019 (Howlader et al. 2019). EEC represents about 80% of EC cases, and over expression of estrogen may contribute to tumor proliferation (Ellenson et al. 2011). Standard of care for EC, regardless of subtype, consists of the surgery followed by adjuvant radiotherapy and/or chemotherapy. In the advanced setting, a variety of endocrine therapy, such as megestrol acetate, tamoxifen, aromatase inhibitors, fulvestrant, are commonly used (NCCN 2020; NCI 2019).

2.2.1. Pharmacokinetics of Imlunestrant

As of 01 November 2021, imlunestrant PK parameters were available from 85 patients in study J2J-MC-JZLA (JZLA) across a 200 to 1200 mg QD dose range. CCI

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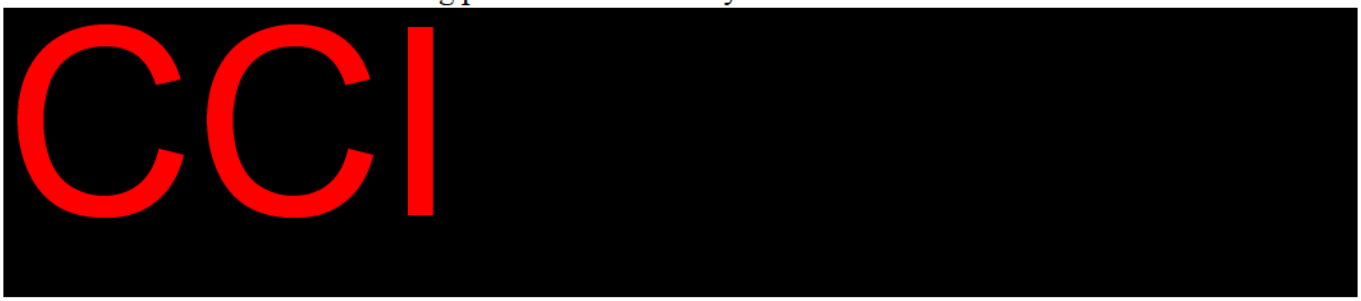
2.3. Benefit/Risk Assessment

Imlunestrant 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 women of non-childbearing potential in this study.



Imlunestrant has also been administered to patients in ongoing clinical studies JZLA (200 to 1200 mg QD for a 28-day cycle) and J2J-MC-JZLB a window of opportunity study (400 and 800 mg) for a period of 15 to 22 days

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As the pharmacologic mechanism of imlunestrant is to degrade the ER, effects on female reproductive organs and embryofetal development are expected. Similar reproductive findings have been observed with other approved agents, known to antagonize or degrade the ER, including tamoxifen (Nolvadex) and fulvestrant (Faslodex®). Therefore, this trial will enroll only women of non-childbearing potential, defined as postmenopausal or infertile due to surgical sterilization or alternate medical cause/congenital anomaly as outlined in Appendix 4 (Section 10.4).

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Genotoxicity

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3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of multiple doses of imlunestrant on the PK of midazolam (CYP3A4 substrate) in healthy women of non-childbearing potential.	AUC(0-∞) and C_{max} of midazolam when administered alone and in the presence of imlunestrant.
Secondary	
• To evaluate the effect of multiple doses of imlunestrant on the PK of 1'-hydroxymidazolam (a metabolite of midazolam) in healthy women of non-childbearing potential. • To evaluate the safety and tolerability of CCI in healthy women of non-childbearing potential. • Evaluate the PK of imlunestrant in healthy women of non-childbearing potential.	• AUC(0-∞) and C_{max} of 1'-hydroxymidazolam when midazolam is administered alone and in the presence of imlunestrant. • Incidence and severity of AEs and SAEs. • AUC(0-24), $_{ss}$ and $C_{max, ss}$ of imlunestrant.

4. Study Design

4.1. Overall Design

Study JZLK is an open-label, fixed sequence, crossover study to investigate the effect of imlunestrant on the PK of midazolam and its metabolite 1'-hydroxymidazolam in healthy women of non-childbearing potential. Additionally, the PK, safety, and tolerability of imlunestrant will also be evaluated.

Safety assessments, including AEs, concomitant medications, physical examination, clinical laboratory tests, vital signs, and electrocardiograms, and blood sampling for PK, will be performed.

4.1.1. Screening

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

4.1.2. Treatment and Assessment Period

Participants will be admitted to the CRU on Day -1 (check-in) and will remain resident until Day 11. With regards to dosing, participants will be dosed as follows:

CCI

There will be a washout period of CCI between doses of midazolam.

4.1.3. Follow-up

Participants will attend a follow-up visit 5 to 7 days post final dose.

4.2. Scientific Rationale for Study Design

The fixed-sequence, crossover design used in 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. In addition, a fixed-sequence design is consistent with FDA guidance.

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

4.3. Justification for Dose

4.3.1. Imlunestrant

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4.3.2. Midazolam

Midazolam is a sensitive CYP3A4 substrate recommended by the FDA for quantifying clinical perpetrator DDI. A CCI may be mildly sedating and high enough to ensure that midazolam concentrations remain above the detection limit of the assay CCI to characterize the CYP3A4 down-regulation potential of imlunestrant. A CCI 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 drug-drug interaction portion of 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, unless otherwise stated in the following criteria.

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. Participants 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, clinical 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).

Sex

6. Female participants:
    a. Women of childbearing potential (WOCBP) are excluded from the trial.
    b. Women not of childbearing potential (WNOCBP) may participate in this trial.

    See Appendix 4 (Section 10.4) for definitions.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2), 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

8. Have known allergies to imlunestrant, related compounds or any components of the formulation or midazolam, as appropriate, or history of significant atopy.
9. 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).
10. History of significant hypersensitivity, intolerance, or allergy to any drug compound including study drugs and any component of their formulations, food, or other substance, unless approved by the investigator (or designee).
11. Have a clinically significant abnormality of blood pressure, pulse rate, or both, as determined by the investigator.
12. Have a history or presence of cardiovascular (for example, 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.
13. History of alcoholism or drug/chemical abuse within 2 years prior to check-in.
14. Alcohol consumption of > 14 units per week. Number of units = [total volume of drink (mL) x alcohol by volume (%)]/1000.
15. Positive ethanol breath/urine test result or positive urine drug screen at screening or check-in.
16. Show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen at screening.
17. Show evidence of hepatitis C and/or positive hepatitis C antibody at screening. A positive result for hepatitis C antibody will be confirmed by polymerase chain reaction test to determine active infection.
18. Have evidence of HIV infection and/or positive human HIV antibodies at screening.
19. Have any medical conditions, medical history, or are taking any medications which are contraindicated in the midazolam label, as appropriate.

Prior/Concomitant Therapy

20. 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).

[redacted]

22. 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).

23. 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

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Prior/Concurrent Clinical Study Experience

25. 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.
26. Have previously completed or withdrawn from this study or any other study investigating imlunestrant, and have previously received imlunestrant.
27. Have previously received a SERD in the past 30 days prior to dosing, or 5 half-lives; whichever is longer.

Other Exclusions

28. 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 from check-in until after collection of the final PK sample.
29. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in.
30. Receipt of blood products within 2 months prior to check-in.
31. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
32. Participants who, in the opinion of the investigator (or designee), should not participate in this study

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

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

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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 follow-up.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

1. Participants will abstain from ingesting caffeine- or xanthine-containing products (for example, coffee, tea, cola drinks, and chocolate) for 48 hours before the initial check-in until after collection of the final PK sample.
2. Participants will abstain from alcohol for 24 hours before the initial 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 initial check-in until after collection of the final PK sample.

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 (for example, watching television, reading).

5.3.4. Other

Imlunestrant demonstrated the potential for phototoxicity in an in vitro study. Participants will be advised to use sunscreen and to wear clothing such as long sleeve tops that cover the arms, pants and/or other garments that cover the legs and hats to cover the head if out in direct sunlight, to reduce the possibility of phototoxicity.

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.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable for this study.

6. Study Intervention(s) and Concomitant Therapy

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 JZLK.1. Study Interventions Administered

Intervention Name	imlunestrant (LY3484356)	midazolam
Type	drug	drug
Dose Formulation	tablet	solution (syrup)
Unit Dose Strength(s)	CCI	-
Dosage Level(s)	CCI	
Route of Administration	Oral	oral
Sourcing	Provided centrally by the sponsor.	Provided locally by the trial site.

6.1.1. Administration Details

Imlunestrant

Imlunestrant CCI All doses of imlunestrant will be administered with 240 mL of room temperature water while participants are in a sitting position. Imlunestrant tablets should be swallowed whole. Participants should not break, crush, or chew the study intervention. On dosing days, participants will adhere to meal restrictions as outlined in Section 5.3.1.

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

Midazolam

A single dose of CCI will be given on Day 1. On Day 9, midazolam will be dosed approximately CCI dosing with CCI imlunestrant. On dosing days, participants will adhere to meal restrictions as outlined in Section 5.3.1.

No additional water is required when midazolam is CCI with imlunestrant on CCI

6.2. Preparation, Handling, Storage, and 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 (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Participants will not be randomized.

6.4. Study Intervention Compliance

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

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 will be provided to the sponsor as requested.

A record of the number of imlunestrant tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Dose Modification

Dose modification will not be permitted in this study.

6.6. Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7. Treatment of Overdose

Any dose of study intervention greater than the dose described for that study day 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 imlunestrant overdose. In the event of midazolam overdose, flumazenil or a similar antagonist for midazolam should be used as an antidote. Activated charcoal may also be used in the event of midazolam overdose.

6.8. Concomitant Therapy

For all participants, 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 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. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Lilly CP/CRP, or designee.

6.8.1. Supportive Management for Diarrhea

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

At the first sign of loose stools, the participant should initiate antidiarrheal therapy (for example, loperamide) and notify the investigator for further instructions and appropriate follow-up. However, loperamide should not be taken the day prior to dosing with midazolam, or on the day of dosing with midazolam.
Participants should also be encouraged to drink fluids (that is, 8 to 10 glasses of clear liquids per day).
Site personnel should assess response within 24 hours.
If diarrhea does not resolve with antidiarrheal therapy within 24 hours to at least Grade 1 (per CTCAE version 5.0 [that is, an increase of <4 stools per day over baseline]), and causes the participant to miss any dose of imlunestrant, the participant should be discontinued from the study.
For severe cases of diarrhea, or any diarrhea associated with severe nausea or vomiting, participants should be carefully monitored and given intravenous fluid and electrolyte replacement as clinically indicated.

- Measurement of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

- If associated with fever or severe neutropenia, further investigations along with broad-spectrum antibiotics such as fluoroquinolones should be considered.

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

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study to complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable and/or will remain in the study and follow procedures for remaining study visits, as shown in the SoA.

A participant should be permanently discontinued from study intervention if in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons

The participant is significantly noncompliant with study procedures and/or treatment.
Unacceptable toxicity.

7.1.1. Liver Chemistry Stopping Criteria

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:

ALT or AST >5× ULN
ALT or AST >3× ULN and 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%)
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 6 (Section 10.6).

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 (Appendix 6 [Section 10.6]; should be considered by the investigator).

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the ○ ○ own request
- at the request of the ○ ○)designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an IP, or enrolled 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 a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA (Section 1.3). If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

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 participant 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 for 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 will be conducted as specified in the schedule of assessments (Section 1.3) and as clinically indicated.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the Schedule of Activities (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 ○ ○ 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.

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

ECGs will be interpreted by a qualified investigator (the physician or qualified designee) as soon after the time of ECG collection as possible, and ideally while the participant is still present, 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. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA 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 or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA and standard collection requirements.

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

8.2.5. Safety Monitoring

8.2.5.1. Hepatic Safety

Close Hepatic Monitoring and Evaluation

Laboratory tests (Appendix 6, Section 10.6), 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	e px))e wx) L × ULN
ALP <1.5 × ULN	e pt) J × ULN
TBL <1.5 × ULN	xf p) J × ULN (except for participants)k ●) :
e px))e wx) IEN× ULN	e px))e wx) J × baseline
e pt) IEN× ULN	e pt) J × baseline
xf p) IEN× ULN	xf p) IEN× baseline (except for participants)k ●) 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 Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), 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))I))L)) Q●○))) ○ ○) ○) ondition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once)I))J) Q)) ○ ○) ○))○) ○●)) ○● E) 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	e px))e wx) L × ULN with hepatic signs/symptoms[a], or e px))e wx) N× ULN
ALP <1.5 × ULN	e pt) L × ULN
TBL <1.5 × ULN	xf p) J × ULN (except for participants)k ●) :)
e px))e wx) IEN× ULN	e px))e wx) J × baseline with hepatic signs/symptoms[a], or e px))e wx) L × baseline
e pt) IEN× ULN	e pt) J × baseline
xf p) IEN× ULN	xf p) J × baseline (except for participants)k ●) :)

[a] 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-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computerized tomography scan).

Based on the ○ ○ history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, ur)) Q)∞) ○ Q)●)○) Q) ○)) glucuronide, and blood phosphatidylethanol. Based on the circumstances and the ○)○))) ○ ○ 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 CRF) in Study Participants Who Have Abnormal Liver Tests During the Study

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

1. Elevation of)e px)) N× ULN on 2 or more consecutive blood tests (if baseline ALT <1.5 × ULN)

   In participants)●○)e px) IEN× ULN, the threshold is ALT L × baseline on 2 or more consecutive tests

2. i ○)xf p)))J × ULN (if baseline TBL <1.5 × ULN) (except for cases of)k ●) :)

   In participants)●○)xf p) IEN× ULN, the threshold should be xf p) J × baseline

3. i ○)))e pt)) J × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN)

   In participants with ●○)e pt) I EN× ULN, the threshold is ALP J × 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
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.

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 ICF	participation in study has ended	as soon as possible upon site awareness	AE CRF	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Serious Adverse Event					
SAE and SAE updates prior to start of study intervention **and** deemed reasonably possibly related to study procedures	signing of the ICF	start of intervention	Within 24 hours of awareness	SAE report	SAE paper form
SAE and SAE updates after start of study intervention	start of intervention	participation in study has ended	Within 24 hours of awareness	SAE report	SAE paper form
SAE* after ○ ○) study participation has ended **and** the investigator becomes aware	after ○ ○) study participation has ended	N/A	Promptly	SAE report	N/A
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information			As soon as possible upon site awareness	Originally completed PC 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	PC form	

* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.4. 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 imlunestrant.
At the visits and times specified in the SoA (Section 1.3), venous blood samples of up to 5 mL each will be collected to determine the plasma concentrations of midazolam and its
○●)I -hydroxymidazolam.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

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.

8.4.1. Bioanalysis

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

Concentrations of imlunestrant, midazolam and 1 -hydroxymidazolam will be assayed using validated liquid chromatography mass spectrometry methods.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this 1 year period, exploratory analyses of drug metabolites in plasma may be conducted.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

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

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable for this study.

8.9. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

The primary endpoints will be evaluated to assess any potential drug-drug interaction between imlunestrant and midazolam.

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

9.2.1. Study Participant Disposition

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

9.2.2. Study Participant Characteristics

The ○ ○)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.

PK analyses will be conducted on data from all participants who received at least 1 dose of IP and have evaluable PK data.

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. AEs 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, and vital signs. 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 imlunestrant will be: $C_{max, ss}$, AUC(0-24), $_{ss}$, and t_{max}. The primary PK parameters for analysis of midazolam and 1 -hydroxymidazolam 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.

9.3.2.2. PK Statistical Inference

PK parameters will be evaluated to estimate the drug-drug interaction between midazolam alone (reference) and midazolam + imlunestrant (test). The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

To estimate the effect of the drug-drug interaction of imlunestrant with midazolam, log-transformed C_{max} and AUC(0- :)of midazolam 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 of test and reference, 90% CIs for the median of differences, and p-values from the Wilcoxon test will be calculated.

Where appropriate, ○ ○ 9I -hydroxymidazolam, and imlunestrant PK 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

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

9.5. Sample Size Determination

CCI

If a participant is discontinued from the study due to an AE of diarrhea causing them to miss any dose of imlunestrant, then that participant should be replaced.

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 International Ethical Guidelines

Applicable ICH Good Clinical Practice Guidelines

The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Informed Consent Process

The investigator or) ○ representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant and is kept on file.

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

10.1.3. 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 the ○ ○ personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

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

The sponsor has processes in place to ensure 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.

10.1.4. 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 ●)○ ○ ○●) ●)))●) ○) ○)) ○ E

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.

10.1.5. Data Quality Assurance

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

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

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

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

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

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

Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in) ○)) ○○●○))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 the sponsor will be encoded and stored in the global product complaint management system.

10.1.6. 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 ○) E

Data reported on or entered in the CRF and 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 10.1.5.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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:

For study termination:

Discontinuation of further study intervention development

For site termination:

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 (evaluated after a reasonable amount of time) of participants by the investigator

Total number of participants included earlier than expected.

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

10.1.8. Publication Policy

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for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.9. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table 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	Bicarbonate (total CO_2)
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes	Glucose
Platelets	Creatine kinase
	Gamma-glutamyl transferase
Coagulation	Blood urea nitrogen
Prothrombin time	Direct bilirubin
Activated partial thromboplastin time	Total protein
International normalized ratio	Albumin
	Total bilirubin
Differential White Blood Cells (absolute and %) of	Alkaline phosphatase
Neutrophils	Aspartate aminotransferase
Lymphocytes	Alanine aminotransferase
Monocytes	Creatinine
Eosinophils	Lipase
Basophils	Amylase
	Uric acid
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,c]
Nitrite	Human immunodeficiency virus antibodies[b]
White blood cell esterase	Follicle-stimulating hormone (if applicable)[b]

[a] Ethanol testing and urine drug screen performed at screening and check-in only.

[b] Performed at screening only.

[c] Positive result will be confirmed by polymerase chain reaction test to determine active infection.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling during the study.

Protocol J2J-MC-JZLK Sampling Summary

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	18.8	1	18.8
Clinical laboratory tests[a]	11	7	77
Pharmacokinetics - imlunestrant[b]	2	11	22
Pharmacokinetics midazolam and I -hydroxymidazolam[b]	5	24	120
Genetic sample	10	1	10
Total			247.8
Total for clinical purposes			250

a Additional samples may be drawn if needed for safety purposes.

b A maximum of 3 samples may be collected at additional timepoints if warranted, as outlined in Section 8.4.

10.3. Appendix 3: Adverse Events and Serious 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 preexisting condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the ○))●))) ○)))) ○ ○) E The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorde)●)))) ○)))) ○ ○) condition. Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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 or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physicia))) ○) setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantia)))○))○●))) normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations: Medical or scientific judgment should be exercised by the investigator 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 PC 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.

PCs related to study interventions used in clinical trials are collected in order to ensure the safety of patients, 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 PC or problem with the study intervention so that the situation can be assessed.
An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC 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/PC 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/PC information in the ○ ○) ○) ○) ○)) ○) ○) ○) practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the PC 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** ○ ○●))) ○)))))) ○ ○) ○) records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC 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 one of the following categories:

Mild: A type of AE 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 AE 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 AE 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.

e))))○))))○) ○)one 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. The investigator will use clinical judgment to determine the relationship

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.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB and/or Product Information, for marketed products, in their 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 their 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 SAE Report

Facsimile transmission of the SAE paper form 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 the SAE report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

The 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, IRB/IEC, and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman not of Childbearing Potential

Females are considered women not of childbearing potential if:

they have a congenital anomaly such as Müllerian agenesis,
they are infertile due to surgical sterilization or alternate medical cause, or
they are postmenopausal.

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

r W○) ○))))))) ○ ○) ○) records, medical examination, or medical history interview.

The postmenopausal state is defined as:

1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or
2. A woman under 60 years of age with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a FSH >40 mIU/mL; or
3. A woman 60 years of age or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea

* Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, GnRH, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may im ○)○) ○ ○)))) susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to imlunestrant or breast/EC and related diseases. They may also be used to develop tests/assays including diagnostic tests related to imlunestrant and breast/EC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to imlunestrant or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on imlunestrant continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

See Section 8.2.5.1 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 (red blood cells)	Alkaline phosphatase
Leukocytes (white blood cells)	Alanine aminotransferase
Differential:	Aspartate aminotransferase
Neutrophils, segmented	Gamma-glutamyl transferase
Lymphocytes	Creatine kinase
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (red blood cells and white blood cells)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol
Prothrombin time, INR	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus testing:	Immunoglobulin IgG (quantitative)
Hepatitis A virus total antibody	Immunoglobulin IgM (quantitative)
Hepatitis A virus IgM antibody	Phosphatidylethanol
Hepatis B virus testing:	**Urine Chemistry**
Hepatitis B surface antigen	Drug screen
Hepatitis B surface antibody	Ethyl glucuronide
Hepatitis B core total antibody	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody
Hepatitis B core IgG antibody	Anti-smooth muscle antibody [a]

Hepatis B virus DNA [b]	Anti-actin antibody [c]
Hepatis C virus testing:	Epstein-Barr virus testing:
Hepatis C virus antibody	Epstein-Barr virus antibody
Hepatis C virus RNA [b]	Epstein-Barr virus DNA [b]
Hepatitis D virus testing:	Cytomegalovirus testing:
Hepatitis D virus antibody	Cytomegalovirus antibody
Hepatitis E virus testing:	Cytomegalovirus DNA [b]
Hepatitis E virus IgG antibody	Herpes simplex virus testing:
Hepatitis E virus IgM antibody	Herpes simplex virus (Type 1 and 2) antibody
Hepatitis E virus RNA [b]	Herpes simplex virus (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 antibody
Culture:	
Blood	
Urine	

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

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

[c] Not required if anti-smooth muscle antibody is tested.

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

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-	area under the concentration versus time curve from time zero to infinity
$AUC_{(0-24),\ ss}$	area under the concentration versus time curve from time zero to 24 hours postdose at steady state
CAP	common alerting protocol
CDK	cyclin-dependent kinase
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, and applicable regulatory requirements.
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
$C_{max,\ ss}$	maximum observed drug concentration at steady state
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
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.
CRU	clinical research unit
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EC	endometrial cancer

ECG	Electrocardiogram
EDC	electronic data capture
EEC	endometrioid endometrial cancer
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ER	estrogen receptor e))
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GnRH	gonadotropin releasing hormone
HIV	human immunodeficiency virus
HR	hormone receptor
HSA	human serum albumin
IB	m ○)Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the ○ ○ decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	investigational product. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

IRB	institutional review board
NIMP	non-investigational medicinal product
OFS	ovarian function suppression
participant	Equivalent to CDISC term ● W○) ○)) ○ ○))○) ○) ○ ○ either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK	pharmacokinetics
QD	once daily
QTc	corrected QT interval
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERD	selective estrogen receptor degrader
SoA	schedule of activities
$t_{1/2}$	half-life associated with the terminal rate constant in non-compartmental analysis
TBL	total bilirubin level
t_{max}	time to maximum plasma concentration
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.
ULN	upper limit of normal

10.8. Appendix 8: Protocol Amendment History

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

11. References

Allison KH, Hammond ME, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-MacGregor M, Perlmutter J, Perou CM, Regan MM, Rimm DL, Symmans WF, Torlakovic EE, Varella L, Viale G, Weisberg TF, McShane LM, Wolff AC. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol.* 2020;38(12):1346-1366.

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

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

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

Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, Francis P, Gligorov J, Kyriakides S, Lin N, Pagani O, Senkus E, Thomssen C, Aapro M, Bergh J, Di Leo A, El Saghir N, Ganza PA, Gelmon K, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Leadbeater M, Mayer M, Rodger A, Rugo H, Sacchini V, Sledge G, van’ t Veer L, Viale G, Krop I, Winer E. 1st international consensus guidelines for advanced breast cancer (ABC 1). Breast. 2012;21(3):242-252.

Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, Verhoeven D, Pedrini JL, Smirnova I, Lichinitser MR, Pendergrass K, Malorni L, Garnett S, Rukazenkov Y, Martin M. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014 Jan;106(1):djt337. doi: 10.1093/jnci/djt337. Epub 2013 Dec 7. PMID: 24317176; PMCID: PMC3906991.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Ellenson LH, Ronnett BM, Kurman RJ. Precursor lesions of endometrial carcinoma. In: Kurman RJ, Ellenson LH, Ronnett BM, editors. *F F F F F F F* . Boston, MA: Springer; 2011:p 359-391.

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

Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD. Based on November 2018 SEER data submission, posted to the SEER web site, April 2019._Available at: https://seer.cancer.gov/csr/1975_2016/. Accessed November 22, 2021.

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

[NCCN] Abu-Rustum NR, Yashar CM, Bean S, Bradley K, Campos SM, Chon HS, Chu C, Clinton L, Cohn D, Crispens MA, Damast S, Fisher CM, Frederick P, Gaffney DK, George S, Giuntoli R 2nd, Han E, Huh WK, Mariani A, Mutch D, Nagel C, Nekhlyudov L, Fader AN, Remmenga SW, Reynolds RK, Sisodia R, Tillmanns T, Ueda S, Urban R, Wyse E, McMillian N, Motter A. NCCN Clinical Practice Guidelines in Oncology Uterine Neoplasms, Version 1.2020 - March 2020.

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

[NCI] National Cancer Institute. PDQ® Adult Treatment Editorial Board. PDQ Endometrial Cancer Treatment. Bethesda, MD. Updated December 2019. Available at: https://www.cancer.gov/types/uterine/hp/endometrial-treatment-pdq. Accessed November 22, 2021.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.

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

van Kruchten M, de Vries EG, Glaudemans AW, van Lanschot MC, van Faassen M, Kema IP, Brown M, Schröder CP, de Vries EF, Hospers GA. Measuring residual estrogen receptor availability during fulvestrant therapy in patients with metastatic breast cancer. Cancer Discov. 2015;5(1):72-81.

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

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

Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol*. 2018;36(20):2105-2122.

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