Protocol Amendment J2J-MC-JZLG (d)

Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment

NCT05440344

Approval Date: 18-Dec-2023

# Title Page



**Protocol Title:** Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment

**Protocol Number:** J2J-MC-JZLG

**Amendment Number:** (d)

**Compound:** Imlunestrant (LY3484356)

**Brief Title:** Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment

**Study Phase:** 1

**Sponsor Name:** Eli Lilly and Company

**Legal Registered Address:** Indianapolis, Indiana 46285, USA

**Regulatory Agency Identifier Number(s)**

IND: 145311

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

**Document ID:** VV-CLIN-074209

**Medical Monitor Name and Contact Information will be provided separately.**

# Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| *Original Protocol* | *07-Jan-2022* |
| *Amendment (a)* | *02-Mar-2022* |
| *Amendment (b)* | *30-Jun-2022* |
| *Amendment (c)* | *18-Sep-2022* |

**Amendment (d)**

**Overall Rationale for the Amendment:**

CCI [redacted] This will allow data from all participants with mild, moderate, and severe hepatic impairment enrolled to date to inform the label at the time of the initial imlunestrant submission. Statistical analysis methods were also updated to provide a more appropriate analysis.

| Section # and Name | Description of Changes | Brief Rationale |
|---|---|---|
| Section 1.1 Synopsis<br>Section 4.1 Overall Design<br>Section 9.4 Interim analysis | CCI [redacted] | CCI [redacted] |
| Section 9.3.4.1 Pharmacokinetic Parameter Estimation | Added that dose normalized parameters may be calculated, as appropriate. | Clarification of methods for analysis of data including participants with severe hepatic impairment. |
| Section 9.3.4.2 Pharmacokinetic Statistical Inference | Replaced paired t-test with details of analysis of covariance method and graphical assessment of the relationship between PK and Child-Pugh classification parameters. | During a planned interim review of data, the planned paired t-test was deemed inappropriate for the analysis. |

**Table of Contents**

## List of Tables

**Table** **Page**

# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title: Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment**

**Brief Title:** Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment

**Regulatory Agency Identifier Number:** IND: 145311

**Rationale:**

Imlunestrant (LY3484356) is an orally bioavailable, non-covalent binding, selective estrogen receptor degrader. It is a potent degrader and selective antagonist of wild-type and mutant estrogen receptor α. This compound is intended for oncology indications (breast cancer and endometrial cancer), in patients where the disease has become less responsive to endocrine therapy, and options are often limited to chemotherapy.

As the intended patient population for imlunestrant may include patients with hepatic impairment, it is important to ascertain how to safely prescribe imlunestrant in this patient population. It is possible that hepatic impairment could lead to a substantial change in the pharmacokinetic (PK) profile of imlunestrant, potentially leading to recommending a dose adjustment to maintain safety, tolerability, and/or efficacy.

A pilot evaluation of the human microsomal cytochrome P450 (CYP)-mediated clearance of imlunestrant by in vitro methods indicated the major role of CYP3A4 in the CYP-mediated oxidative metabolism. Independently, uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes involved in the formation of the *O*-glucuronide metabolite were investigated using recombinant human enzymes. The involvement of UGT1A1 and 1A8 and to a lesser extent UGT1A3, 1A9 and 1A10 were identified based on the unbound intrinsic clearance per milligram of total protein. The magnitude of the contribution of CYP3A4 and different UGTs toward the overall clearance of imlunestrant is unknown since the in vivo clearance pathways of imlunestrant have not yet been determined. However, prior experience with drugs metabolized by these pathways suggests that a reduction in activity of the CYP and UGT enzymes may occur in hepatic insufficiency. This study will be conducted to evaluate the PK of imlunestrant in participants with impaired hepatic function based on Child-Pugh hepatic impairment classifications of mild, moderate, and severe. The tolerability of imlunestrant will also be assessed. The design is in alignment with the Food and Drug Administration guidance recommendation for studies when hepatic metabolism and/or excretion accounts for >20% of the elimination of a parent drug or active metabolite.

Notable changes in PK as a result of hepatic impairment identified in this study will be considered with emerging exposure-safety/tolerability or response relationships from patient trials to determine the need for dosage adjustment in the hepatically impaired patient population.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the PK of imlunestrant in women of non-childbearing potential with hepatic impairment compared to control women of non-childbearing potential with normal hepatic function. | Plasma concentration data (total) should be analyzed to estimate measures or parameters describing the PK of imlunestrant (e.g., area under the concentration versus time curve, maximum observed drug concentration) after a single CCI (or lower) imlunestrant dose. |
| **Secondary** | |
| To evaluate the tolerability of imlunestrant in women of non-childbearing potential with hepatic impairment and control women of non-childbearing potential with normal hepatic function. | Incidence of treatment-emergent adverse events and serious adverse events. |

**Overall Design**

**Brief Summary:**

Study JZLG is an open-label, single-dose study. The study will be conducted in up to 4 groups: Group 1: participants with normal hepatic function (Control); Group 2: participants with mild hepatic impairment (Child-Pugh A); Group 3: participants with moderate hepatic impairment (Child-Pugh B); and Group 4: participants with severe hepatic impairment (Child-Pugh C).

Participants with normal hepatic function and mild hepatic impairment can be dosed concurrently from the onset of the study. A review to assess imlunestrant safety and PK will be conducted after at least 3 participants with mild hepatic impairment have completed all PK sampling; imlunestrant will not be administered to participants with moderate hepatic impairment until the review has been completed. CCI imlunestrant will not be administered to participants with severe hepatic impairment until this analysis and review have been completed. Additional reviews to assess imlunestrant safety and PK will be conducted after 3 participants with severe hepatic impairment have completed all PK sampling.

CCI

A final analysis will be conducted and a clinical study report produced after all cohorts have completed all PK samples, unless no further participants with severe hepatic impairment are enrolled after production of the interim clinical study report.

Group 1 (normal hepatic function) will be matched by age (±10 years), sex, and body mass index (BMI, ±15%) to participants either in Group 2 (mild hepatic impairment) or Group 3 (moderate hepatic impairment) as far as reasonably possible but allowing timely completion of the study. Reasonable attempts will be made to match Group 4 (severe hepatic impairment) participants with the other groups.

Group 3 and/or 4 participants may be omitted if safety results indicate important clinically significant safety concerns. Control participants (Group 1) may be enrolled in parallel with participants in Groups 2, 3, and 4. The demographics of these 6 control participants will be selected to ensure the best chance of matching demographics of hepatically impaired participants in Group 2 and Group 3, based on historical data from the study sites.

Participants who do not complete dosing and PK sampling may be replaced in order to target 6 completers for hepatic impairment Groups 2, 3, and 4, and a minimum of 6 and maximum of 12 completers for the control group; these numbers may be reduced if the study objectives are met earlier.

Attempts will be made to recruit and dose 6 severe hepatic impairment participants; however, recruiting participants with severe hepatic impairment (Child-Pugh C) may be difficult. The sponsor may elect to complete fewer than 6 participants in Group 4 if the study sites cannot recruit sufficient numbers for this group. In addition, Cohorts 2 and 3 may be expanded to include a total of 9 participants, dependent on the results from Cohort 4.

Safety assessments, including adverse events, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and electrocardiograms, and blood sampling for PK, will be performed.

**Screening**

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

**Treatment and Assessment Period**

Eligible participants will participate in 1 treatment period. Participants will be admitted to the clinical research unit (CRU) on Day -1. All participants will receive a single dose of CCI (or lower for hepatically impaired participants) imlunestrant on Day 1 in the fasted state. Participants may either remain resident in the CRU until discharge on Day 5, and attend outpatient visits on each of Days 6 through 11; or may remain resident in the CRU until discharge on Day 11.

If it becomes necessary for the participant to leave the study site during this period, continued participation may be allowed at the discretion of the investigator if they are felt to be able to comply with study procedures and restrictions without negative impact to safety or study integrity.

**Follow-up**

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

**Study Population:**

Participants will be at least 18 years old and will be included if they are either healthy or have mild, moderate, or severe hepatic impairment. Participants with hepatic impairment must have had a diagnosis of chronic hepatic impairment and no clinically significant changes within 90 days before dosing with study drug. These participants may have other medical conditions that are mild and that would not affect the health of the participant or the study conduct.

**Number of Participants:**

The study will be conducted in up to 4 groups, based on the Child-Pugh classification of hepatic impairment, as follows:

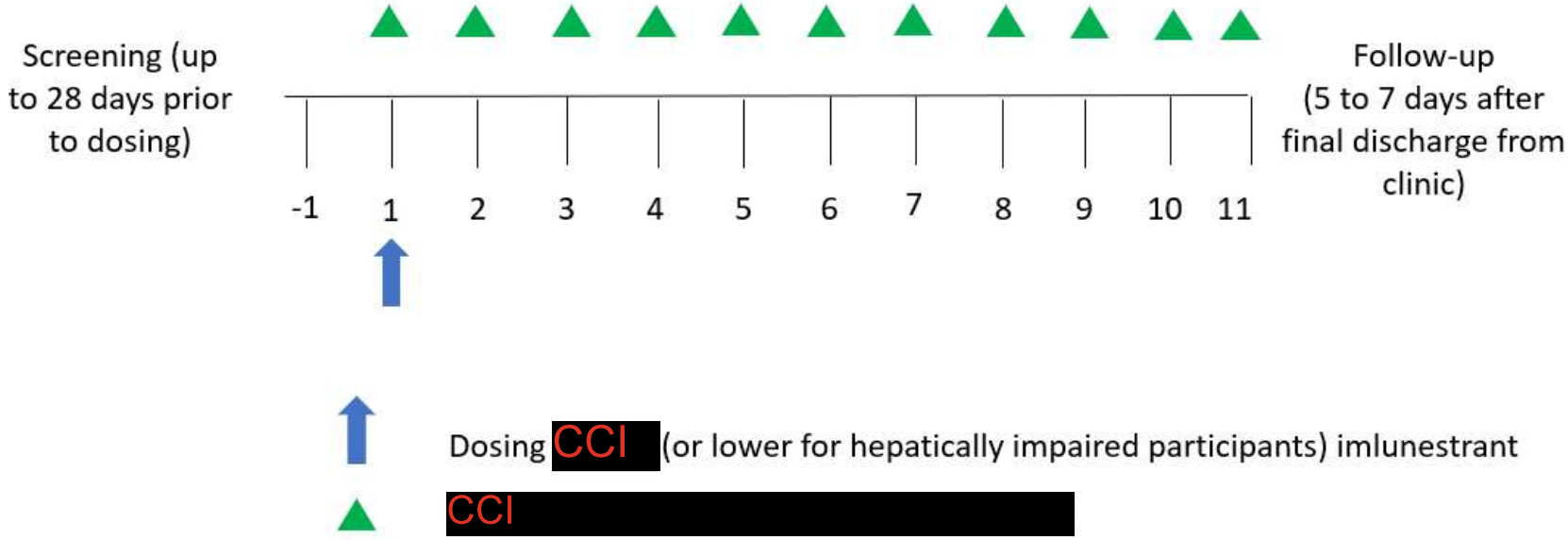
- **Group 1:** participants with normal hepatic function (Control); minimum of [redacted] and maximum of [redacted] completers
- **Group 2:** participants with mild hepatic impairment (Child-Pugh A); [redacted] completers
- **Group 3:** participants with moderate hepatic impairment (Child-Pugh B); [redacted] completers
- **Group 4:** participants with severe hepatic impairment (Child-Pugh C); [redacted] completers

**Intervention Groups and Duration:**

This study will be conducted in 4 groups; each participant is expected to participate in the study for up to 44 to 46 days.

**Data Monitoring Committee:** No

## 1.2. Schema




Abbreviation: PK = pharmacokinetic.

## 1.3. Schedule of Activities (SoA)

| Procedure | Screening (up to 28 days before Day 1) | Treatment Period[a] | | | | | | | | | | | | Follow-up (5 to 7 days post final CRU discharge) or ED | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | | |
| Informed consent | X | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria including Child-Pugh Classification | X | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | |
| Full physical examination including height and weight | X | | P | | | | | | | | | | X | X | After screening, medical assessment only performed to include medical review and targeted examination, as appropriate. |
| Medical history | X | | | | | | | | | | | | | | |
| Past and current medical conditions | X | | | | | | | | | | | | | | |
| Urinary drugs of abuse | X | X | | | | | | | | | | | | | |
| Ethanol breath test | X | X | | | | | | | | | | | | | |
| Study intervention | | | X | | | | | | | | | | | | |
| Laboratory assessments | X | X | P | X | | | X | | | X | | | X | X | |

| Procedure | Screening (up to 28 days before Day 1) | Treatment Period[a] -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | Follow-up (5 to 7 days post final CRU discharge) or ED | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12-lead electrocardiogram | X | | P | | X | | X | | | X | | | X | X | |
| Vital sign (supine) | X | X | P, 2, 4, 6, 8, 10, 12h | X | X | X | X | X | X | X | X | X | X | X | |
| CCI | | | | | | | | | | | | | | | |
| Genetic sample | | | X | | | | | | | | | | | | |
| Adverse event/Serious adverse event review | X | X | ←========== | ========== | ========== | ========== | ========== | ========== | ========== | ========== | ========== | ========== | ==========→ | X | |
| Concomitant medication review | X | X | ←========== | ========== | ========== | ========== | ========== | ========== | ========== | ========== | ========== | ========== | ==========→ | X | |

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; P = predose; PK = pharmacokinetic; SAE = serious adverse event.

Note: Participants may either remain resident in the CRU from admission on Day -1 until discharge on Day 5, and attend outpatient visits on each of Days 6 through 11, or may remain resident in the CRU until discharge on Day 11.

# 2. Introduction

Imlunestrant (LY3484356) is an orally bioavailable, non-covalent, SERD. It is a potent degrader and selective antagonist of wild-type and mutant Erα (or ESR1). This compound is intended for oncology indications (breast cancer and endometrial cancer), 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

As the intended patient population for imlunestrant may include patients with hepatic impairment, it is important to ascertain how to safely prescribe imlunestrant in this patient population. It is possible that hepatic impairment could lead to a substantial change in the PK profile of imlunestrant, potentially leading to recommending a dose adjustment to maintain safety, tolerability, and/or efficacy.

A pilot evaluation of the human microsomal CYP-mediated clearance of imlunestrant by in vitro methods indicated the major role of CYP3A4 in the CYP-mediated oxidative metabolism. Independently, UGT enzymes involved in the formation of the *O*-glucuronide metabolite were investigated using recombinant human enzymes. The involvement of UGT1A1 and 1A8 and to a lesser extent 1A3, 1A9, and 1A10 were identified based on the unbound intrinsic clearance per milligram of total protein. The magnitude of the contribution of CYP3A4 and different UGTs toward the overall clearance of imlunestrant is unknown because the in vivo clearance pathways of imlunestrant have not yet been determined. However, prior experience with drugs metabolized by these pathways suggests that a reduction in activity of the CYP and UGT enzymes may occur in hepatic insufficiency. This study will be conducted to evaluate the PK of imlunestrant in participants with impaired hepatic function based on Child-Pugh hepatic impairment classifications of mild, moderate, and severe. The tolerability of imlunestrant will also be assessed. The design is in alignment with the FDA guidance recommendation for studies when hepatic metabolism and/or excretion accounts for >20% of the elimination of a parent drug or active metabolite. Albumin concentrations may be lower in people with hepatic impairment than in people with normal hepatic function. Therefore, it will be important to measure the unbound concentration of imlunestrant in this study because of its high protein-binding ability.

Notable changes in PK as a result of hepatic impairment identified in this study will be considered with emerging exposure-safety/tolerability or response relationships from patient trials to determine the need for dosage adjustment in the hepatically impaired patient population.

## 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. Hormone receptor-positive 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 (e.g., tamoxifen, anastrozole, letrozole, fulvestrant) alone or in combination CDK4 and CDK6 inhibitors as indicated (e.g., abemaciclib, palbociclib, or ribociclib), as well as standard chemotherapy (e.g., capecitabine, docetaxel, paclitaxel, and nab-paclitaxel [NCCN 2018; Waks and Winer 2019]). For patients with advanced HR+/HER2+ status, treatment includes HER2-directed therapies (e.g., trastuzumab, pertuzumab, trastuzumab emtansine 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 CCI 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). Endometrioid EC represents about 80% of EC cases, and overexpression 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 (NCI 2019; NCCN 2020).

### 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 CCI QD dose range. After single oral administration, maximum plasma concentrations of imlunestrant were reached approximately 4 hours postdose. The mean $t_{1/2}$ was approximately 25 to 30 hours and exposures of imlunestrant increased with dose. The fasted exposures (AUC and $C_{max}$) of healthy participants in study J2J-MC-JZLD (JZLD) were within range of the fasted exposures observed in patient studies after the same doses.

A pilot study of protein binding was conducted in vitro using equilibrium dialysis in human plasma, human liver microsomes, and solutions of human alpha-1-acid glycoprotein and HSA

protein. Imlunestrant was CCI bound in human plasma and CCI bound in human liver microsomes. Binding to human CCI was less than that observed CCI. The binding to CCI was consistent with binding observed in human plasma.

The in vitro metabolism of imlunestrant was evaluated in human liver microsomes, intestine microsomes, and hepatocytes. Imlunestrant displayed low intrinsic clearance in liver microsomes in the presence of nicotinamide adenine dinucleotide phosphate, with minimal oxidative metabolism being observed. However, the metabolism of imlunestrant in both liver and intestinal microsomes was greater in the presence of uridine diphosphate glucuronic acid, with formation of a direct glucuronide conjugate being observed. In the human hepatocyte incubations, metabolites from direct glucuronidation and sulfation were predominant while minor metabolites from CYP mediated oxidation were also observed.

The preliminary analysis of study JZLD indicated that the AUC and $C_{max}$ of imlunestrant were increased by approximately 2-fold in a drug-drug interaction study with itraconazole. This is consistent with a significant but not dominant role of CYP3A4 in the bioavailability and/or hepatic clearance of imlunestrant.

## 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.

Due to the early stage of the development of imlunestrant, the clinical safety profile has not been fully established. There are currently ongoing clinical studies in healthy participants (JZLD and J2J-MC-JZLE [JZLE]). As of 01 November 2021, study JZLD has a total of 38 healthy female participants. In this study, participants receive CCI of CCI imlunestrant (Cohorts 1, 2, and 4), or CCI single doses of CCI imlunestrant (Cohort 3). Study JZLE has 5 healthy female participants that are receiving a single dose of CCI imlunestrant (Parts 1 or 2). These studies are still ongoing.

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

As of 01 November 2021, 134 patients have received imlunestrant monotherapy (N=22, CCI; N=64, CCI; N=20, CCI; N=25, CCI; and N=3, CCI) in study JZLA. No dose-limiting toxicities have been reported at any of the dose levels tested. Imlunestrant was well tolerated across dose levels in dose escalation, and a maximum tolerated dose was not reached. In the 134 patients receiving JZLA monotherapy (all dose levels), the most frequently reported TEAEs were nausea (46 [34%]), fatigue (37 [28%]), and diarrhea (36 [27%]). Most TEAEs were Grade 1 or 2 in severity. Grade ≥3 events were observed in 19 patients (14%). There were 10 SAEs reported in 7 patients (5.2%) who received imlunestrant monotherapy (all dose levels). Of note, 1 patient reported SAEs of diarrhea and nausea, which were considered by the investigator to be related to study treatment. The remaining SAEs were considered not related to imlunestrant, being mostly likely due to underlying disease, preexisting conditions, or concomitant medications. No maximum tolerated dose was established during dose escalation.

Given the totality of efficacy, clinical PK, and safety data, the sponsor is proceeding into additional clinical trials with the CCI QD dose level.

Overall, the majority of TEAEs were low grade, monitorable, manageable and reversible. The risk to participants receiving the CCI dose is considered low, as only 1 dose of imlunestrant will be received in this study and the patients will be closely monitored as documented in the SoA.


Non-reproductive imlunestrant-related toxicities have demonstrated partial to full reversibility.

As the pharmacologic mechanism of imlunestrant is to degrade the ER, effects on female reproductive organs are expected. Similar female reproductive tract 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).

Potential toxicities will be regularly monitored during this study through ongoing assessment of participant symptoms, hematological and chemistry levels, and ECG readings, as detailed in Section 8.2. Participants will also 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, CCI [redacted].

**Genotoxicity**

Imlunestrant was negative for mutagenicity in the Ames assay. It was positive for chromosomal damage in vitro in the presence of metabolic activation CCI [redacted] via a mixed, predominantly aneugenic mechanism. The chromosomal damage observed in vitro occurred at levels of imlunestrant higher than participants will receive. In vivo, imlunestrant did not induce chromosomal damage in rats CCI [redacted] (Table JZLG.2). The high threshold concentration for *in vitro* aneugenicity and the lack of chromosomal damage *in vivo* represent a weight of evidence indicating that the risk of imlunestrant *in vivo* genotoxicity is low, in accordance with ICH S2, and establishes safe exposures for clinical trial participants, including healthy participants. The risk to healthy participants in the present study is further reduced by administration of 1 dose of imlunestrant.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of imlunestrant may be found in the IB.

# 3. Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the PK of imlunestrant in women of non-childbearing potential with hepatic impairment compared to control women of non-childbearing potential with normal hepatic function. | Plasma concentration data (total) should be analyzed to estimate measures or parameters describing the PK of imlunestrant (e.g., AUC, $C_{max}$), after a single CCI (or lower) imlunestrant dose. |
| **Secondary** | |
| To evaluate the tolerability of imlunestrant in women of non-childbearing potential with hepatic impairment and control women of non-childbearing potential with normal hepatic function. | Incidence of TEAEs and SAEs. |

# 4. Study Design

## 4.1. Overall Design

Study JZLG is an open-label, single-dose study.

The study will be conducted in up to 4 groups, based on the Child-Pugh classification of hepatic impairment (Child and Turcotte, 1964; Pugh et al. 1973):

- **Group 1:** participants with normal hepatic function (Control); minimum of [redacted] and maximum of [redacted] completers
- **Group 2:** participants with mild hepatic impairment (Child-Pugh A); [redacted] completers
- **Group 3:** participants with moderate hepatic impairment (Child-Pugh B); [redacted] completers
- **Group 4:** participants with severe hepatic impairment (Child-Pugh C); [redacted] completers.

The Child-Pugh system of hepatic impairment is provided in Table JZLG.1.

**Table JZLG.1. Child-Pugh System of Hepatic Impairment**

| Parameter | 1 Point | 2 Points | 3 Points |
|---|---|---|---|
| Serum albumin (g/dL) | >3.5 | 2.8 to 3.5 | <2.8 |
| Total serum bilirubin (mg/dL) | <2.0 | 2.0 to 3.0 | >3.0 |
| Prolonged prothrombin time (sec)<br>or<br>Prothrombin time INR (ratio) | <4<br><br><1.70 | 4 to 6<br><br>1.70 to 2.30 | >6<br><br>>2.30 |
| Ascites[a] | Absent | Slight<br>or<br>Subject on 1 medication to control ascites | Moderate<br>Or<br>Subject on 2 medications to control ascites |
| Hepatic encephalopathy[b] | None | 1 or 2<br>Or<br>Current treatment with lactulose or neomycin | 3 or 4<br>Or<br>Continued encephalopathy while receiving treatment with lactulose and/or neomycin |

Child-Pugh System of Hepatic Impairment: Adapted from Child and Turcotte, 1964, Pugh et al, 1973.
Child-Pugh A: 5 or 6 points; Child-Pugh B: 7 to 9 points; Child-Pugh C: 10 to 15 points (scores are the sum of the 5 parameters).
Abbreviations: INR = international normalized ratio (subject prothrombin time/normal plasma pool prothrombin time).
a Ascites is graded according to the following criteria:
Absent: No ascites detectable by manual investigation.
Slight: Ascites palpation doubtful.
Moderate: Ascites detectable by palpation.
Severe: Necessity of paracentesis, does not respond to medication treatment.
b State of hepatic encephalopathy is graded according to investigator assessment used at the site.

The schema in Section 1.2 illustrates the study design. Participants with normal hepatic function and mild hepatic impairment can be dosed concurrently from the onset of the study. A review to assess imlunestrant safety and PK will be conducted after at least 3 participants with mild hepatic impairment have completed all PK sampling; imlunestrant will not be administered to participants with moderate hepatic impairment until the review has been completed. CCI [redacted] imlunestrant will not be administered to participants with severe hepatic impairment until this analysis and review have been completed. Additional reviews to assess imlunestrant safety and PK will be conducted after 3 participants with severe hepatic impairment have completed all PK sampling.

CCI [redacted]

A final analysis will be conducted and a clinical study report produced after all cohorts have completed all PK samples, unless no further participants with severe hepatic impairment are enrolled after production of the interim clinical study report. Further information is provided in Section 9.4.

Group 1 (normal hepatic function) will be matched by age (±10 years), sex, and BMI ±15% to participants either in Group 2 (mild hepatic impairment) or Group 3 (moderate hepatic impairment) as far as reasonably possible but allowing timely completion of the study. Reasonable attempts will be made to match Group 4 (severe hepatic impairment) participants with the other groups.

Group 3 and/or 4 participants may be omitted if safety results indicate important clinically significant safety concerns. Control participants (Group 1) may be enrolled in parallel with participants in Groups 2, 3, and 4. The demographics of these [redacted] control participants will be selected to ensure the best chance of matching demographics of hepatically impaired participants in Group 2 and Group 3, based on historical data from the study sites.

Participants who do not complete dosing and PK sampling may be replaced in order to target [redacted] completers for hepatic impairment Groups 2, 3, and 4, and a minimum of [redacted] and maximum of [redacted] completers for the control group; these numbers may be reduced if the study objectives are met earlier.

Attempts will be made to recruit and dose 6 severe hepatic impairment participants; however, recruiting participants with severe hepatic impairment (Child-Pugh C) may be difficult. The sponsor may elect to complete fewer than [redacted] participants in Group 4 if the study sites cannot recruit sufficient numbers for this group. In addition, Cohorts 2 and 3 may be expanded to include a total of [redacted] participants, dependent on the results from Cohort 4.

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

#### 4.1.1. Screening

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

#### 4.1.2. Treatment and Assessment Period

Eligible participants will participate in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive a single dose of CCI (or lower for hepatically impaired participants) imlunestrant on Day 1 in the fasted state. Participants may either remain resident in the CRU until discharge on Day 5, and attend outpatient visits on each of Days 6 through 11, or may remain resident in the CRU until discharge on Day 11.

If it becomes necessary for the participant to leave the CRU during this period, continued participation may be allowed at the discretion of the investigator if they are felt to be able to comply with study procedures and restrictions without negative impact to safety or study integrity.

#### 4.1.3. Follow-up

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

### 4.2. Scientific Rationale for Study Design

This study has been designed in accordance with the FDA regulatory guidance for the study of PK in participants with impaired hepatic function.

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

A single-dose, parallel design is the standard design to investigate the PK of a drug in participants with hepatic impairment. A parallel design is required to include participants with hepatic impairment and control participants with normal hepatic function. Control healthy participants with normal hepatic function will be enrolled in this study to serve as a reference group for interpretation of the results. The safety and PK assessments are standard parameters for clinical studies in drug development.

Healthy females of non-childbearing potential have been selected as the study population since the pharmacologic mechanism of imlunestrant is to degrade the ER, and effects on the female reproductive organs are expected.

### 4.3. Justification for Dose

The clinical safety experience from study JZLA is described in Section 2.3. Imlunestrant was well tolerated at dose levels of CCI with no dose-limiting toxicities in Cycle 1. No maximum tolerated dose was established during dose escalation. Given the totality of efficacy, clinical PK, and safety data, the sponsor has selected the CCI dose level to be evaluated in planned patient trials.

The recommended Phase 3 dose of CCI will be used, though may be reduced within a hepatic impairment group and for subsequent groups based on review of safety and PK data.

In vitro studies indicate that imlunestrant undergoes oxidation by CYP3A4 and glucuronidation by UGT1A1, UGT1A8, UGT1A3, UGT1A9, and UGT1A10. The relative contribution of these

enzymes to imlunestrant bioavailability and/or clearance in humans is unknown. Preliminary analysis of data from study JZLD indicates that imlunestrant $C_{max}$ and AUC were increased approximately 2-fold, indicating a significant, but not dominant, role of CYP3A4 in bioavailability and/or hepatic clearance.

As described in the IB and Section 2.3, the nonclinical safety profile of imlunestrant is characterized primarily by pharmacologically mediated female reproductive organ toxicity. Adverse findings unrelated to the reproductive tract have not been observed up to the highest dose tested in monkeys or the highest tolerated dose in rats. Based on observed mean $C_{max}$ and AUC over the last 24-hour dosing interval at CCI and CCI in study JZLA (Table JZLG.2). Imlunestrant exposures in this study are expected to maintain an appropriate margin of safety relative to key toxicities.

Across all dose levels, the majority of events were low grade, monitorable, reversible, and manageable, the most frequent being gastrointestinal effects (nausea and diarrhea), and fatigue. Specifically at doses over CCI (CCI N=20; CCI N=25; and CCI N=3), the majority of TEAEs reported were also low grade, with a similar incidence of Grade ≥3 TEAEs as observed at the CCI dose level. One patient reported SAEs of diarrhea and nausea, which were considered by the investigator to be related to study treatment.

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

**Table JZLG.2. Exposure Margins in Rat and Monkey Toxicity Studies Relative to Observed Clinical PK Following a Single Dose of CCI Imlunestrant**

| Species | Animal or Human Dose Level | $C_{max}$ (ng/mL) | $C_{max}$ Margin | | $AUC_{0-\infty}$ (ng·h/mL) | AUC Margin | |
|---|---|---|---|---|---|---|---|
| | | | CCI | CCI | | CCI | CCI |
| Human | CCI | CCI | | | | | |
| Rat | Non-reproductive NOAEL CCI /kg/day[b]<br>LOAEL reproductive toxicity CCI /kg/day[b]<br>LOAEL maternal, EFD toxicity CCI /kg/day[c]<br>NOEL in vivo micronucleus CCI /kg/day[d]<br>STD10 CCI /kg/day[e] | | | | | | |
| Monkey | Non-reproductive NOAEL, HNSTD CCI /kg/day[f]<br>LOAEL reproductive toxicity CCI /kg/day[f] | | | | | | |

Abbreviations: EFD = embryofetal development; HNSTD = highest non-severely toxic dose; LOAEL = lowest-observed adverse effect level; NOAEL = no-observed adverse effect level; NOEL = no-observed effect level.

[a] Geometric mean clinical PK data following a single dose administration of CCI (N=23) CCI (N=18) imlunestrant in Study JZLA (data cut 01 November 2021)

[b] Determined in 3-month rat toxicity study (Study 8003221); end-of-study male-female average exposures.

[c] Determined in enhanced rat embryofetal development pilot study (Study 9001840).

[d] Exposures measured on Day 2 of a confirmatory toxicokinetics study (Study 8451175) under the same experimental conditions as the in vivo rat micronucleus assay.

[e] Determined in 4-week rat toxicity study (Study 8002568); end-of-study male-female average exposures.

[f] Determined in 3-month monkey toxicity study (Study 8003147); end-of-study male-female average exposures.

## 4.4. End of Study Definition

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

The end of the study is defined as the date of the last visit of the last participant in the study.

# 5. Study Population

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

The nature of any conditions present at the time of the physical examination and any preexisting 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:

**Inclusion Criteria Applicable to ALL Participants:**

***Age***

1. participant must be at least 18 years at the time of signing the informed consent.

***Type of Participant***

2. participants who have venous access sufficient to allow for blood sampling as per the protocol.

***Weight***

3. BMI within the range 18.0 to 42.0 kg/m$^2$ (inclusive).

***Sex***

4. female participants of non-childbearing potential as defined in Appendix 4 (Section 10.4)

***Informed Consent***

5. capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

**Additional Inclusion Criteria for Control Participants (Group 1)**

6. participants who are overtly healthy as determined by medical assessment including medical history, physical examination, laboratory tests, and vital signs
7. 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

**Additional Inclusion Criteria for Participants with Hepatic Impairment (Groups 2 to 4)**

8. individuals with hepatic impairment classified as Child-Pugh class A, B, or C (mild, moderate or severe impairment; Child and Turcotte 1964; Pugh et al. 1973) who are considered acceptable for participation in this study by the investigator. Participants must have diagnosis of chronic hepatic impairment (>6 months), with no clinically significant changes within 90 days prior to study drug administration (Day 1). Participants may have

mild stable baseline medical conditions for which neither the condition nor treatments received would negatively affect the health of the participant or study conduct.

9. clinical laboratory test results with deviations that are judged by the investigator to be compatible with the hepatic impairment of the participant, or are of no additional clinical significance for this study

## 5.2. Exclusion Criteria

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

**Exclusion Criteria for ALL Participants:**

10. are investigational site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
11. are Lilly employees

***Medical Conditions***

12. have known allergies to imlunestrant, related compounds or any components of the formulation, as appropriate, or history of significant atopy
13. significant history or clinical manifestation of any metabolic, allergic, dermatological, pulmonary, or psychiatric disorder, as determined by the investigator (or designee)
14. history of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee)
15. have a clinically significant abnormality of blood pressure and/or pulse rate as determined by the investigator
16. have a history or presence of cardiovascular, 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
17. history of alcoholism or drug/chemical abuse within 2 years prior to check-in
18. alcohol consumption of >14 units per week. One unit of alcohol equals 1/2 pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits
19. positive ethanol breath/urine test result or positive urine drugs of abuse screen at screening or check-in
20. have evidence of HIV infection and/or positive human HIV antibodies.
21. have donated blood of more than 500 mL within the previous 2 months of study screening
22. have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
23. have had breast cancer within the past 10 years
24. hepatocellular cancer unless treated by locoregional therapy that demonstrates ablation without evidence of recurrent hepatocellular cancer >1 year prior to check-in
25. have severe encephalopathy (Grade 3 to 4)

***Prior/Concomitant Therapy***

26. use or intend to use medications that are strong inhibitors or inducers of CYP3A4 within 14 days prior to dosing until completion of the follow-up visit. Exceptions to the 2-week restriction may be allowed on a case-by-case basis and only after review and approval by the Lilly clinical pharmacologist, clinical research physician, or designee.

***Prior/Concurrent Clinical Study Experience***

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

***Diagnostic Assessments***

30. 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 approximately 2 hours prior to and 2 hours post dosing
31. ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to check-in
32. receipt of blood products within 2 months prior to check-in
33. donation of plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening
34. participants who, in the opinion of the investigator (or designee), should not participate in this study

**Additional Exclusions for Control Participants (Group 1)**

35. show evidence of positive hepatitis B surface antigen, as confirmed with HBV DNA. Participants who test positive for hepatitis B surface antigen may be included if they do not have active infection, as confirmed by a polymerase chain reaction test
36. show evidence of hepatitis C and/or positive hepatitis C antibody. Participants who test positive for hepatitis C antibody may be included if they do not have active infection, as confirmed by a polymerase chain reaction test
37. 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)
38. use or intend to use any prescription medications/products within 14 days prior to dosing until completion of the follow-up visit, unless deemed acceptable by the investigator (or designee)
39. 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)
40. use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in until completion of the follow-up visit, unless deemed acceptable by the investigator (or designee)

41. current or chronic history of liver disease or known hepatic or biliary abnormalities

**Additional Exclusion Criteria for Participants with Hepatic Impairment (Groups 2 to 4)**

42. evidence of any significant active disease other than that responsible for or associated with hepatic impairment that would significantly affect the ability of the participant to safely participate in the trial, in the opinion of the investigator
43. have creatinine clearance ≤50 mL/min using the Cockcroft and Gault formula
44. evidence of spontaneous bacterial peritonitis within 3 months of dosing
45. have had variceal bleeding within 3 months of check-in (unless banded)
46. evidence of severe hyponatremia (sodium approximately <120 mmol/L)
47. have severe ascites
48. presence of an active portal shunt, or newly placed shunt (within the last 6 months).
49. have hemoglobin <9.0 g/dL
50. have serum bilirubin >15 mg/dL
51. have used concomitant medication known to interfere with hepatic metabolism (such as barbiturates, phenothiazines,) or known to alter other major organs or systems within 2 weeks prior to dosing
52. regularly use drugs of abuse and/or have positive findings on urinary drug screen, except those prescribed for the treatment of liver disease or related complications (e.g., pain, insomnia, anxiety).

## 5.3. Lifestyle Considerations

### 5.3.1. Meals and Dietary Restrictions

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

Imlunestrant will be dosed in the fasted state. Participants will be fasted overnight (at least CCI ) prior to dosing and refrain from consuming water from CCI predose until CCI postdose, excluding the amount of water consumed at dosing. Food is allowed from CCI postdose. At all other times during the study, participants may consume water ad libitum.

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

### 5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK sample.
- Participants will abstain from alcohol for 24 hours before the check-in until after collection of the final PK sample.
- Participants are required to refrain from smoking more than 10 cigarettes or using the equivalent in tobacco, smoking-cessation products, nicotine-containing products, per day, and e-cigarettes (nicotine and non-nicotine) from check-in and through final

discharge from the CRU. Participants must be willing to abstain from smoking approximately 2 hours prior to and 2 hours post dosing.

### 5.3.3. Activity

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

### 5.3.4. Other

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.

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

# 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

This table lists the interventions used in this study.

**Table JZLG.3. Study Interventions Administered**

| Intervention Name | imlunestrant (Groups 1, 2, 3, and 4) |
|---|---|
| **Authorized as defined by EU CTR[a]** | Not authorized as defined by EU CTR |
| **Unit Dose Strength(s)/ Dosage Level(s)** | CCI tablets (CCI imlunestrant) |
| **Route of Administration** | Oral |

Abbreviation: CTR = Clinical Trials Regulations

[a] Authorized means a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of the labeling, packaging, and whether CT or commercial material is being supplied.

### Packaging and Labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

### 6.1.1. Administration Details

All doses of imlunestrant will administered with approximately CCI of room temperature water while in a sitting position.

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

Participants will not be allowed to lie supine for CCI after dosing, unless clinically indicated or for study procedures.

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

## 6.2. Preparation, Handling, Storage, and Accountability

- 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.
- 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.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- 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, non-randomized study.

## 6.4. Study Intervention Compliance

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

## 6.5. Dose Modification

CCI [redacted]

## 6.6. Continued Access to Study Intervention after the End of the Study

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

## 6.7. Treatment of Overdose

For this study, any dose of imlunestrant greater than CCI within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator or treating physician should

- Contact the Lilly CP immediately
- 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.

## 6.8. Concomitant Therapy

Participants in Groups 2 to 4 who are on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. Participants will be asked to delay dosing of any concomitant medications from 2 hours prior, until 4 hours after dosing of imlunestrant on study Day 1, unless this delay is not deemed to be appropriate by the investigator for the participant's medical condition.

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.

# 7. Participant Discontinuation/Withdrawal

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

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

## 7.1. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at her own request
- at the request of her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

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

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

### 7.1.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from the study treatment. If the investigator and the Lilly CP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study. Safety follow-up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events, Serious Adverse Events, and Product Complaints) of the protocol.

## 7.2. Lost to Follow Up

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

# 8. Study Assessments and Procedures

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

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

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

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

## 8.1. Efficacy Assessments

Not applicable.

## 8.2. Safety Assessments

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

### 8.2.1. Physical Examinations

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

### 8.2.2. Vital Signs

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

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

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

### 8.2.3. Electrocardiograms

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

Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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

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

### 8.2.4. Clinical Safety Laboratory Tests

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

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

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

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements.

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

### 8.2.5. Safety Monitoring

#### 8.2.5.1. Hepatic Safety

**Close hepatic monitoring**

Laboratory tests (Appendix 5, Section 10.5), including ALT, AST, ALP, TBL, direct bilirubin, GGT, and CK, 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 <1.5x ULN | ALT or AST ≥3x ULN |
| ALP <1.5x ULN | ALP ≥2x ULN |
| TBL <1.5x ULN | TBL ≥2x ULN (except for patients with Gilbert's syndrome) |
| ALT or AST ≥1.5x ULN | ALT or AST ≥2x baseline |
| ALP ≥1.5x ULN | ALP ≥2x baseline |
| TBL ≥1.5x ULN | TBL ≥1.5x baseline (except for patients with Gilbert's syndrome) |

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the 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 frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

**Comprehensive hepatic evaluation**

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

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

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

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

**Additional hepatic data collection (hepatic safety 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 4 conditions:

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

Note: The interval between the two consecutive blood tests should be at least 2 days.

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

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

- AEs
- SAEs
- Product complaints

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.

### 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 |
| **Serious Adverse Event** | | | | | |
| SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures | signing of the ICF | start of intervention | Within 24 hours of awareness | SAE paper form | SAE paper form |
| SAE and SAE updates – after start of study intervention | start of intervention | participation in study has ended | Within 24 hours of awareness | SAE paper form | SAE paper form |
| SAE* – after participant's study participation has ended **and** the investigator becomes aware | After participant's study participation has ended | N/A | Promptly | SAE paper form | N/A |
| **Product Complaints** | | | | | |
| PC associated with an SAE or might have led to an SAE | Start of study intervention | End of study intervention | Within 24 hours of awareness | Product Complaint form | N/A |

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-up Method of Reporting |
|---|---|---|---|---|---|
| PC not associated with an SAE | Start of study intervention | End of study intervention | Within 1 business day of awareness | Product Complaint form | N/A |
| Updated PC information | — | — | As soon as possible upon site awareness | Originally completed Product Complaint form with all changes signed and dated by the investigator | N/A |
| PC (if investigator becomes aware) | Participation in study has ended | N/A | Promptly | Product Complaint form | |

Abbreviations: AE = adverse event; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

* Serious adverse events 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 and venous blood samples of up 10 mL will be collected to determine CCI [redacted].

Up to 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

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

### 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 will be assayed using a validated liquid chromatography mass spectrometry method. The unbound concentration in plasma will also be measured. Samples collected for the analysis of plasma concentrations of imlunestrant may be stored and analyzed for future exploratory analysis.

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

## 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

## 9.1. Statistical Hypotheses

This study will evaluate the PK of imlunestrant in women of non-childbearing potential with hepatic impairment compared to control women of non-childbearing potential with normal hepatic function.

## 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 1 dose of IP. |
| Pharmacokinetic Analysis | All participants who received 1 dose of IP and have evaluable PK. |

### 9.2.1. Study Participant Disposition

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

### 9.2.2. Study Participant Characteristics

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

### 9.2.3. Treatment Compliance

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

## 9.3. Statistical Analysis

### 9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee. Additional exploratory analysis of the data will be conducted as deemed appropriate.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in SAP, where appropriate. Adjustments to the planned analyses are described in the final clinical study report.

### 9.3.2. Clinical Evaluation of Safety

All investigational product 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 investigational product as perceived by the investigator. Adverse events reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

### 9.3.3. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

### 9.3.4. Pharmacokinetic Analyses

#### 9.3.4.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates will be calculated by standard noncompartmental methods.

The primary PK parameters for analysis of imlunestrant (total) will be $AUC_{0-\infty}$, $AUCt_{last}$, and $C_{max}$, or their equivalent dose normalized parameters, as appropriate. Other noncompartmental parameters, such as $t_{1/2}$, CL/F, and $Vd_z/F$, may be reported as appropriate. The impact of hepatic impairment on plasma protein binding of imlunestrant will be summarized using descriptive statistics of plasma protein binding data.

#### 9.3.4.2. Pharmacokinetic Statistical Inference

A statistical analysis will be conducted to evaluate the PK of imlunestrant following a single dose in participants with mild, moderate, or severe hepatic impairment (test) compared to matched healthy participants with normal hepatic function (reference function) for primary PK parameters ($AUC_{0-\infty}$, $AUCt_{last}$, and $C_{max}$).

Statistical analysis to compare each test hepatic function participant to their corresponding reference hepatic function participant will be performed separately. The PK parameters $AUC_{0-\infty}$, $AUCt_{last}$, and $C_{max}$ will be analyzed in logarithmic scale using an analysis of covariance model with hepatic function group as a fixed effect and body weight as a covariate. The difference between each test (hepatic impairment) group and the reference (normal hepatic function) group will be presented. The 90% confidence interval for the geometric mean ratio between each test group versus the reference group will be presented.

The relationship between the PK and Child-Pugh classification parameters Child-Pugh score, serum albumin concentration, total bilirubin concentration, and prothrombin time will also be assessed graphically.

Further details of these analyses are provided in the SAP.

## 9.4. Interim Analysis

Participants with normal hepatic function and mild hepatic impairment can be dosed concurrently from the onset of the study.

A review (not an interim analysis) to assess imlunestrant safety and PK will be conducted after at least 3 participants with mild hepatic impairment have completed all PK sampling. Study enrollment can continue in Groups 1 and 2 during the review but imlunestrant will not be administered to participants with moderate hepatic impairment until the review has been completed.

Another review along with an interim analysis will be conducted after data from 6 participants with mild hepatic impairment (Group 2) and 6 participants with moderate hepatic impairment (Group 3) have been obtained. The SAP will describe the planned interim analyses in greater detail. The timing of dissemination of data summaries based on interim analyses is addressed in Appendix 1, Section 10.1.5. Study enrollment can continue in Groups 1 through 3 during the interim analysis and review but imlunestrant will not be administered to participants with severe hepatic impairment until this analysis and review have been completed. Additional reviews to assess imlunestrant safety and PK will be conducted after 3 participants with severe hepatic impairment have completed all PK sampling.

CCI [redacted]

A final analysis will be conducted and a clinical study report produced after all cohorts have completed all PK samples, unless no further participants with severe hepatic impairment are enrolled after production of the interim clinical study report.

The dose of 400 mg imlunestrant may be reduced within a hepatic impairment group and for subsequent groups based on review of safety and PK data. Doses may be reduced based on the magnitude of any differences in exposure observed between the control group and hepatically impaired participants.

Additional data reviews may occur at any time if deemed appropriate based on safety, tolerability, or PK information.

## 9.5. Sample Size Determination

Overall, up to approximately 35 participants may be enrolled to ensure 24 completers, as follows:

- **Group 1:** participants with normal hepatic function (Control); minimum of 6 and maximum of 12 completers
- **Group 2:** participants with mild hepatic impairment (Child-Pugh A); 6 completers
- **Group 3:** participants with moderate hepatic impairment (Child-Pugh B); 6 completers
- **Group 4:** participants with severe hepatic impairment (Child-Pugh C); 6 completers.

# 10. Supporting Documentation and Operational Considerations

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

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - Applicable laws and regulations
- 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
    - Reporting significant issues related to participant safety, participant rights, or data integrity
- Investigational sites are compensated for participation in the study as detailed in the clinical trial agreement.

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

- The investigator or the investigator's 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.

### 10.1.4. Data Protection

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

### 10.1.5. Dissemination of Clinical Study Data

**Communication of Suspended or Terminated Dosing**

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

**Reports**

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

**Data**

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

### 10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic 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 (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the 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 the 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 systems will be stored at third-parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. 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 the central vendor's database system and electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

### 10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on 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 10.1.6.

### 10.1.8. 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 and/or follow-up.

### 10.1.9. Publication Policy

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

### 10.1.10. 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 |
| | Uric acid |
| Activated partial thromboplastin time | Total protein |
| International normalized ratio | Albumin |
| | Total bilirubin |
| **Differential White Blood Cells (absolute counts) of** | Alkaline phosphatase |
| Neutrophils | Aspartate aminotransferase |
| Lymphocytes | Alanine aminotransferase |
| Monocytes | Creatinine |
| Eosinophils | Lipase |
| Basophils | Amylase |
| **Urinalysis** | |
| Specific gravity | |
| pH | |
| Protein | |
| Glucose | Ethanol testing[a] |
| Ketones | Urine drug screen[a] |
| Bilirubin | Hepatitis B surface antigen[b,c,d] |
| Urobilinogen | Hepatitis B DNA[b,d] |
| Blood | Hepatitis C antibody[b,c,d] |
| Nitrite | Human immunodeficiency virus antibodies[b] |
| | Follicle-stimulating hormone (if applicable)[b] |

[a] 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.
[d] Control Participants (Group 1) only.

### 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-JZLG 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 (total) [b] | 2 | 21 | 42 |
| Pharmacokinetics CCI [b] | 10 | 3 | 30 |
| Genetic sample | 10 | 1 | 10 |
| Total | | | 177.8 |
| Total for clinical purposes | | | 180 |

[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).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical 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 investigator to be more severe than expected for the participant's condition.<br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.<br>• Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE. |

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

### 10.3.2. Definition of SAE

**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 physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

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

**e. Is a congenital anomaly/birth defect**

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

**f. Other situations:**

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

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

**AE, SAE, and Product Complaint Recording**

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

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

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

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

  An event is defined as 'serious' when it meets at least 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 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.

### 10.3.5. Reporting of SAEs

**SAE Reporting via Paper Form**

- 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**

- 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 (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

**Definitions:**

**Woman not of Childbearing Potential**

Females are considered women not of childbearing potential if:

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

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

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

The post-menopausal 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 at least 40 years of age and up to 55 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 follicle-stimulating hormone >40 mIU/mL; or
3. A woman 55 years of age or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone-replacement therapy.

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

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

See protocol 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] |

| **Hematology** | **Clinical Chemistry** |
|---|---|
| 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.

## 10.6. Appendix 6: Abbreviations and Definitions

| Term | Definition |
|---|---|
| **abuse** | Use of a study intervention for recreational purposes or to maintain an addiction or dependence |
| **AE** | adverse event |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **AST** | aspartate aminotransferase |
| **AUC** | area under the concentration versus time curve |
| **$AUC_{0-\infty}$** | area under the concentration versus time curve from time zero extrapolated to infinity |
| **$AUC_{tlast}$** | area under the concentration versus time curve from time zero to the last quantifiable concentration |
| **BMI** | body mass index |
| **CFR** | Code of Federal Regulations |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **CK** | creatine kinase |
| **CL/F** | apparent clearance |
| **$C_{max}$** | maximum observed plasma concentration |
| **CMV** | cytomegalovirus |
| **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, GCP, and applicable regulatory requirements. |
| **CP** | clinical pharmacologist |
| **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. |

| Term | Definition |
|---|---|
| **CRU** | clinical research unit |
| **CT** | computed tomography |
| **CYP** | cytochrome P450 |
| **DMC** | data monitoring committee. A data monitoring committee, or data monitoring board is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. |
| **EBV** | Epstein-Barr virus |
| **EC** | endometrial cancer |
| **EDC** | electronic data capture |
| **ECG** | electrocardiogram |
| **enroll** | The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment. |
| **enter** | Participants entered into a study are those who sign the ICF directly or through their legally acceptable representatives. |
| **ER** | estrogen receptor |
| **FDA** | Food and Drug Administration |
| **GCP** | good clinical practice |
| **GGT** | gamma-glutamyl transferase |
| **HDV** | hepatitis D virus |
| **HIV** | human immunodeficiency virus |
| **HR** | hormone receptor |
| **HER2** | human epidermal growth factor receptor 2 |
| **HSA** | human serum albumin |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IEC** | independent ethics committee |

| Term | Definition |
|---|---|
| **Ig** | immunoglobulin |
| **IMP** | Investigational Medicinal Product (see also "investigational product")<br>A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. |
| **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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated ICF. |
| **INR** | international normalized ratio |
| **interim analysis** | An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked. |
| **investigational product (IP)** | 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 |
| **medication error** | Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time.<br>In addition to the core five rights, the following may also represent medication errors:<br>• dose omission associated with an AE or a product complaint<br>• dispensing or use of expired medication<br>• use of medication past the recommended in-use date<br>• dispensing or use of an improperly stored medication<br>• use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or<br>• shared use of cartridges, prefilled pens, or both. |
| **misuse** | Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription |
| **NIMP** | Non-investigational Medicinal Product. See AxMP.<br>A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. |

| Term | Definition |
|---|---|
| **participant** | Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control |
| **PC** | product complaint |
| **PK/PD** | pharmacokinetic(s)/pharmacodynamics |
| **PT** | prothrombin time |
| **QD** | once daily |
| **QTc** | corrected QT interval |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| **SERD** | selective estrogen receptor degrader |
| **$t_{1/2}$** | half-life |
| **TBL** | total bilirubin |
| **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. |
| **UGT** | uridine 5'-diphospho-glucuronosyltransferase |
| **ULN** | upper limit of normal |
| **$Vd_z/F$** | apparent volume of distribution |

## 10.7. Appendix 7: Protocol Amendment History

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

**Amendment (c): 18 September 2022**

This amendment is considered to be substantial because it is likely to have a significant impact on the reliability and robustness of the data generated in the clinical study.

**Overall Rationale for the Amendment:**

The protocol was amended to increase the number of completers from 3 to 6 in both the mild and moderate hepatic impairment groups. CCI [redacted] These additions will aid in having the mild and moderate hepatic impairment data to inform the label at the time of the initial imlunestrant submission.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1 Synopsis | Updated timing of data reviews and added information regarding an interim analysis. | The interim analysis will provide finalized data for participants with mild and moderate hepatic damage for the submission. |
| | Updated the target number of completers in Groups 2 and 3 to "[redacted]" in the context of replacing participants who do not complete dosing and PK sampling.<br>Increased the number of participants that Cohorts 2 and 3 may be expanded to include from "[redacted]" to "[redacted]."<br>Updated the number of completers in Group 2 with mild hepatic impairment from "[redacted]" to "[redacted]."<br>Updated the number of completers in Group 3 with moderate hepatic impairment from "[redacted]" to "[redacted]". | To increase the reliability and robustness of the data generated in the study. |
| Section 4.1 Overall Design | Updated the number of completers in Group 2 with mild hepatic impairment from "[redacted]" to "[redacted]." | To increase the reliability and robustness of the data generated in the study. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Updated the number of completers in Group 3 with moderate hepatic impairment from "[redacted]" to "[redacted]."<br>Updated the target number of completers in Groups 2 and 3 to "[redacted]" in the context of replacing participants who do not complete dosing and PK sampling.<br>Increased the number of participants that Cohorts 2 and 3 may be expanded to include from "[redacted]" to "[redacted]."<br>Updated the timing of data reviews and added information regarding an interim analysis. | The interim analysis will provide finalized data for participants with mild and moderate hepatic damage for the submission. |
| [redacted] | [redacted] | [redacted] |
| Section 9.5 Sample Size Determination | Updated the overall number of participants enrolled to "[redacted]" and number of overall completers to "[redacted]."<br>Updated the number of completers in Group 2 with mild hepatic impairment from "[redacted]" to "[redacted]."<br>Updated the number of completers in Group 3 with moderate hepatic impairment from "[redacted]" to "[redacted]." | To increase the reliability and robustness of the data generated in the study. |
| Section 11 References | Added one reference. | The reference was inadvertently left off of the reference list. |
| Throughout | Editorial changes made. | |

**Amendment (b): 30 June 2022**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1, Synopsis, Section 1.2, Schema, Section 1.3, Schedule of Activities, and Section 4.1.2 Treatment and Assessment Period | Flexibility surrounding length of stay in the clinical research unit was added to the study design. | To aid recruitment. |
| Section 1.1, Synopsis, Section 4.1, Overall Design, and Section 9.5, Sample Size Determination | Number of completers in Group 1 updated. | To allow flexibility in matching with Groups 2 through 4. |
| Section 1.1, Synopsis, Section 1.2, Schema, Section 1.3, Schedule of Activities, and Section 4.1.3 Follow-up | Follow-up now specified as 5 to 7 days post final CRU discharge. | For clarity. |
| Section 5.2, Exclusion Criteria | Exclusions #16, #31, and #42 amended.<br>Exclusion #43 was removed.<br>New exclusions added as #22, #23, #24, and #25. | Per site request.<br>Per site and team requests. |
| Section 5.3.1, Meals and Dietary Restrictions, and Section 5.3.2, Substance Use: Caffeine, Alcohol, and Tobacco | Clarified that 'discharge' as used in these sections is referring to final discharge from the CRU. | For clarity. |
| Section 6.8, Concomitant Therapy | Timing for which concomitant medications should be restricted prior to dosing added. | Per site request. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.2, Appendix 2: Clinical Laboratory Tests | Hepatitis B core antibody test removed. Hepatitis B Virus DNA test added.<br>Footnoted that hepatitis tests are applicable to control participants only. | Per site request.<br>For clarity. |
| Section 10.2.1, Blood Sampling Summary | Addition of blood volume table. | Unintentionally omitted from original protocol. |

**Amendment (a): 02 March 2022**

**Overall Rationale for the Amendment**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1, Synopsis | Regulatory agency identifier and lay summaries of study population were added. | As advised by European Union Clinical Trials Regulations questions and answers, published October 2021. |
| Section 1.1, Synopsis | Removal of pharmacokinetic parameter estimation of unbound imlunestrant. | Descriptive statistics of plasma protein binding data will be presented instead. |
| Section 1.3, Schedule of Activities | Pharmacokinetic sampling timepoints for unbound imlunestrant were updated. | Unbound concentrations are only needed at certain timepoints. |
| Section 2.1, Study Rationale | Removal of repeated information from Section 2. | Unintentionally duplicated in original protocol. |
| | Rationale for measurement of unbound imlunestrant added. | Unintentionally omitted from original protocol. |
| Section 2.2.1, Pharmacokinetics of Imlunestrant | Addition of summary of pharmacokinetic findings from Study JZLD, a drug-drug interaction study with itraconazole. | New data available at the time of protocol amendment. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 3, Objectives and Endpoints | Removal of pharmacokinetic parameter estimation of unbound imlunestrant. | Descriptive statistics of plasma protein binding data will be presented instead. |
| Section 4.3, Justification for Dose | Addition of summary of pharmacokinetic findings from Study JZLD, a drug-drug interaction study with itraconazole. | New data available at the time of protocol amendment. |
| Section 5.2, Exclusion Criteria | Clarified that participants who test positive for hepatitis B surface antigen or hepatitis C antibody may be included if they are negative by polymerase chain reaction testing. | Intent of exclusion criteria was to exclude participants with active infection. Participants may still be positive for hepatitis B surface antigen or hepatitis C antibody without active infection. This can be confirmed by polymerase chain reaction testing. |
| Section 6.1, Study Intervention(s) Administered | Reorganization and clarification of information related to the study intervention. | Requirements of European Union Clinical Trials Regulations 536/2014 Article 59(2) and Annex 1 (17 [b]) |
| 8.2.5, Safety Monitoring<br>8.2.5.1, Hepatic Safety | Added language for safety monitoring in case of hepatic abnormalities. | Unintentionally omitted from original protocol. |
| Section 8.4, Pharmacokinetics | Pharmacokinetic sampling methods for unbound imlunestrant were updated. | Unbound concentrations are only needed at certain timepoints. |
| Section 9.3.1, General Considerations | Added statement regarding handling is missing, unused or spurious data. | Requirements of European Union Clinical Trials Regulations 536/2014 Annex 1 (17 [u]) |
| Section 9.3.4.1, Pharmacokinetic Parameter Estimation | Removal of pharmacokinetic parameter estimation of unbound imlunestrant. | Descriptive statistics of plasma protein binding data will be presented instead. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.1.1, Regulatory and Ethical Considerations | Added additional investigator responsibilities. | Requirements of European Union Clinical Trials Regulations 536/2014 |
| Section 10.1.5, Dissemination of Clinical Study Data | Added information related to dissemination of summary of results. | Requirements of European Union Clinical Trials Regulations 535/2014 Article 37 (8) and Annex I (17 [aj]). |
| Section 10.2, Appendix 2: Clinical Laboratory Tests | Clarified that participants who test positive for hepatitis B surface antigen or hepatitis C antibody may have a polymerase chain reaction test to confirm active infection. | Participants may still be positive for hepatitis B surface antigen or hepatitis C antibody without active infection. This can be confirmed by polymerase chain reaction testing. |
| Section 10.3.1, Definition of an Adverse Event | Updates to definition of events meeting the adverse event definition. | Requirements of European Union Clinical Trials Regulations 536/2014 Annex III (2.1 [2]). |
| 10.5, Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments | Added actions and follow-up items in case of hepatic abnormalities. | Unintentionally omitted from original protocol. |

# 11. References

André F, Ciruelos E, Rubovszky G, et al.; SOLAR-1 Study GROUP. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. https://doi.org/10.1056/NEJMoa1813904

Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520-529. https://doi.org/10.1056/NEJMoa1109653

Bray F, Ferlay J, Soerjomatram I, et al. 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. https://doi.org/10.3322/caac.21492

Cardoso F, Costa A, Norton L, et al. 1st international consensus guidelines for advanced breast cancer (ABC 1). Breast. 2012;21(3):242-252.

Child, C. and Turcotte, J. Surgery and Portal Hypertension. Major Problems in Clinical Surgery, 1964;1, 1-85.

Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst*. 2014;106(1):djt337. https://doi.org/10.1093/jnci/djt337

Ellenson LH, Ronnett BM, Kurman RJ. Precursor lesions of endometrial carcinoma. In: Kurman RJ, Ellenson LH, Ronnett BM, editors. *Blaustein's Pathology of the Female Genital Tract*. Boston, MA: Springer; 2011:p 359-391.

Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med.* 2016;375(20):1925-1936. https://doi.org/10.1056/NEJMoa1607303

Howlader N, Noone AM, Krapcho M, et al. 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. Accessed November 22, 2021. https://seer.cancer.gov/csr/1975_2016/

Nardone A, Weir H, Delpuech O, et al. 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. https://doi.org/10.1038/s41416-018-0354-9

[NCCN] Abu-Rustum NR, Yashar CM, Bean S, et al. NCCN Clinical Practice Guidelines in Oncology Uterine Neoplasms, Version 1.2020 - March 2020.

[NCCN] Gradishar WJ, Anderson BO, Aft R, et al. 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. Accessed November 22, 2021. https://www.cancer.gov/types/uterine/hp/endometrial-treatment-pdq

Pugh RN, Murray-Lyon IM, Dawson JL, Pietrini MC, Williams R. Transection of the esophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646–649.

Turner NC, Ro J, André F, et al.; PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2015;373(3):209-219. https://doi.org/10.1056/NEJMoa1505270

van Kruchten M, de Vries EG, Glaudemans AW, et al. Measuring residual estrogen receptor availability during fulvestrant therapy in patients with metastatic breast cancer. *Cancer Discov*. 2015;5(1):72-81. https://doi.org/10.1158/2159-8290.CD-14-0697

Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA.* 2019;321(3):288-300. https://doi.org/10.1001/jama.2018.1932

Weatherman RV, Fletterick RJ, Scanlan TS. Nuclear-receptor ligands and ligand-binding domains. *Annu Rev Biochem.* 1999;68:559-581. https://doi.org/10.1146/annurev.biochem.68.1.559

Signature Page for VV-CLIN-074209 v2.0

| | |
|---|---|
| Approval | PPD<br>15-Dec-2023 13:53:35 GMT+0000 |

| | |
|---|---|
| Approval | PPD<br>18-Dec-2023 16:09:46 GMT+0000 |

Signature Page for VV-CLIN-074209 v2.0