Protocol J2J-MC-JZLI (a)

The Effect of Imlunestrant on CYP2C8, CYP2C19, CYP2D6, P-gp, and BCRP Activity and the Effect of P-gp Inhibition on Imlunestrant Pharmacokinetics in Healthy Women of Non-childbearing Potential

NCT05444556

Approval Date: 26-Jun-2022

Title Page

Protocol Title:

The Effect of Imlunestrant on CYP2C8, CYP2C19, CYP2D6, P-gp, and BCRP Activity and the Effect of P-gp Inhibition on Imlunestrant Pharmacokinetics in Healthy Women of Non-childbearing Potential

Protocol Number: J2J-MC-JZLI

Amendment Number: (a)

Compound: Imlunestrant (LY3484356)

Brief Title: A study to investigate imlunestrant CYP and Transporter DDIs

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 (a) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-062530

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*12-April-2022*

Amendment (a)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 4.1.2 Treatment and Assessment Period	For Cohort 3, clarified that participants will not be in the CRU on Days 9 to 13, and will not dose at home.	For accuracy.
	For Cohort 3, Clarified that in order for AEs to be reported spontaneously, that participants will call the CRU in the event of an AE.	For clarity
	For Cohort 4, added that participants will attend the CRU as outpatients on Days 6 through 8.	For accuracy
Section 1.2 Schema	Screening window updated.	For consistency with the Schedule of Assessments.
	For Cohort 4, added that participants will attend the CRU as outpatients on Days 6 through 8.	For accuracy.
Section 1.3 Schedule of Assessments	Added that ECGs taken on Day -1 in Cohorts 1 and 4 may be taken any time after check-in.	For clarity.
	Added posture of supine for all ECG assessments in all cohorts.	For clarity.

Section # and Name	Description of Change	Brief Rationale
	Added timing of genetic sample (to be taken at Day 1 predose) for all cohorts.	For clarity.
	Weight separated from physical examination into a new row for each cohort.	For clarity.
	For Cohort 3, clarified that in order for AEs to be reported spontaneously on Days 9 to 13, that participants will call the CRU in the event of an AE.	For clarity.
	For Cohort 4, added row for outpatient visits.	For accuracy.
	For Cohort 4, the genetic sample was moved from Day -1 to Day 1.	
Section 6.1 Study Interventions Administered	Dose formulation for dextromethorphan was updated from capsule to oral suspension, and number of capsules required, and the unit dose strength was removed.	Dextromethorphan oral suspension will now be used instead of the capsule formulation. An oral suspension is being used due to difficulty in acquiring the capsule formulation.
Section 6.1.1 Administration Details	Clarified that the oral suspension of dextromethorphan will be administered via oral dosing syringe instead of an oral capsule, alongside the number and volume of rinses for the oral dosing syringe. Also clarified the timing of dosing with imlunestrant, omeprazole, and dextromethorphan on Day 3.	In alignment with the change in formulation of dextromethorphan.
Section 8 Study Assessments and Procedures	The order of assessments at individual timepoints was added.	For clarity.
Section 8.4 Pharmacokinetics	Blood and urine sampling information split out into separate bullet points.	For clarity
Section 9.4 Interim Analysis	Clarified that the interim analysis will be performed after Cohort 2.	For accuracy.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

The Effect of Imlunestrant on CYP2C8, CYP2C19, CYP2D6, P-gp, and BCRP Activity and the Effect of P-gp Inhibition on Imlunestrant Pharmacokinetics in Healthy Women of Non-childbearing Potential

Brief Title: A study to investigate imlunestrant CYP and Transporter DDIs

Rationale:

Study J2J-MC-JZLI (JZLI) is a Phase 1 open-label, 4-cohort study of imlunestrant administered to healthy females of non-childbearing potential. In vitro data indicates that imlunestrant has the potential to inhibit cytochrome P450 (CYP)2C8, CYP2C19, CYP2D6, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) and clinical studies are required to quantify this potential effect. The FDA guidance on drug-drug interactions (DDIs) recommend repaglinide, omeprazole, and dextromethorphan as sensitive probes of CYP2C8, CYP2C19, and CYP2D6, respectively. Similarly, digoxin and rosuvastatin are recommended probes for quantify inhibition of P-gp and BCRP. Therefore, the purpose of this study is to investigate the effect of imlunestrant on CYP2C8, CYP2C19, and CYP2D6, and P-gp and BCRP activity by use of repaglinide, omeprazole, dextromethorphan, and digoxin and rosuvastatin, respectively. In vitro data also identified imlunestrant as a substrate of P-gp. The FDA recommends quinidine as a relatively selective inhibitor of P-gp when compared to other P-gp inhibtors that target CYP3A4 in addition to P-gp. Therefore, to investigate the effect of P-gp inhibition on imlunestrant this study will employ repeat dosing of quinidine to inhibit both intestinal and central P-gp activity (liver, kidney, or both). The results of this study will inform dosing instructions in ongoing patient trials.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Cohort 1: Evaluate the effect of imlunestrant on the pharmacokinetics (PK) of repaglinide (CYP2C8 substrate) in healthy women of non-childbearing potential.	• Cohort 1: Area under the concentration versus time curve from zero to infinity (AUC[0-∞]), maximum observed drug concentration (C_{max}) of repaglinide administered alone and in the presence of imlunestrant.
• Cohort 2: Evaluate the effect of imlunestrant on the PK of omeprazole	• Cohort 2: AUC(0-∞), C_{max} of omeprazole, 5-hydroxyomeprazole,

(CYP2C19 substrate) and dextromethorphan (CYP2D6 substrate) in healthy women of non-childbearing potential. • Cohort 3: Evaluate the effect of quinidine (P-gp inhibitor) on the PK of imlunestrant in healthy women of non-childbearing potential. • Cohort 4: Evaluate the effect of imlunestrant on the PK of rosuvastatin (BCRP substrate) and digoxin (P-gp substrate) in healthy women of non-childbearing potential.	dextromethorphan and dextrorphan administered alone and in the presence of imlunestrant. • Cohort 3: AUC(0-∞), C_{max} of imlunestrant administered alone and in the presence of quinidine. • Cohort 4: AUC(0-∞), C_{max} of rosuvastatin and digoxin administered alone and in the presence of imlunestrant.
Secondary	
• To evaluate the safety and tolerability of 400 and 800 mg imlunestrant in healthy females of non-childbearing potential.	• Incidence and severity of adverse events (AEs) and serious AEs

Overall Design

Brief Summary:

Study JZLI is an open-label, 4-cohort, study comprising 4 fixed-sequence crossover cohorts. Cohorts 1 to 4 are in healthy females of non-childbearing potential to investigate the effect of imlunestrant on the PK of repaglinide (Cohort 1), omeprazole and dextromethorphan (Cohort 2), and rosuvastatin and digoxin (Cohort 4), and to investigate the effect of quinidine on the PK of imlunestrant (Cohort 3). Additionally, the safety and tolerability of imlunestrant will be evaluated when administered as a single 800-mg oral dose in the presence of repaglinide or omeprazole and dextromethorphan, and as a single oral 400-mg dose in the presence of quinidine or rosuvastatin and digoxin.

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

Study Population:

Participants will be healthy women not of childbearing potential, aged between 18 and 65 years, inclusive.

Number of Participants:

In Cohorts 1, 2, and 4, approximately 27 participants should be enrolled to ensure that at least 22 evaluable participants in each of these cohorts complete the study. In Cohort 3, approximately 32 participants should be enrolled to ensure that at least 26 evaluable participants in this cohort complete the study.

Intervention Groups and Duration:

Screening

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

Treatment and Assessment Period

Cohort 1 – imlunestrant on CYP2C8 activity

Cohort 1 will be an open-label, fixed-sequence design evaluating the effect of imlunestrant on CYP2C8. Participants will be admitted to the clinical research unit (CRU) on Day -1. All participants will receive:

- **Day 1:** 0.5 mg repaglinide alone
- **Day 3:** 800 mg imlunestrant + 0.5 mg repaglinide

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

Cohort 2 – imlunestrant on CYP2C19 and CYP2D6 activity

Cohort 2 will be an open-label, fixed-sequence design evaluating the effect of imlunestrant on CYP2C19 and CYP2D6. Participants will be admitted to the CRU on Day -1. All participants will receive:

- **Day 1:** 20 mg omeprazole and 30 mg dextromethorphan
- **Day 3:** 800 mg imlunestrant + 20 mg omeprazole and 30 mg dextromethorphan

There will be a washout period of 2 days between doses of omeprazole and dextromethorphan. All participants will remain resident in the CRU until discharge on Day 5.

Cohort 3 – P-gp inhibition on imlunestrant

Cohort 3 will be an open-label, fixed-sequence design evaluating the effect of P-gp on imlunestrant. Eligible participants will take part in 2 treatment periods. Participants will be admitted to the CRU on Day -1. All participants will receive:

- **Day 1:** 400 mg imlunestrant
- **Days 15 to 17:** 200 mg quinidine twice daily (BID) alone
- **Day 18:** 400 mg imlunestrant + 200 mg quinidine BID
- **Day 19 to Day 24:** 200 mg quinidine bid alone

There will be a washout period of 17 days between doses of imlunestrant. All participants will remain resident in the CRU until discharge on Day 8, then will be re-admitted to the CRU on Day 14 until Day 25.

On Days 9 to 13, participants will not be in the CRU. During this time, AEs and concomitant medications will be reported spontaneously by the participant. Participants will be instructed to call the CRU in the event of an AE. If the participant does need to take concomitant medication, they must contact the CRU so that the PI and CP may consult and approve the concomitant medication prior to the participant taking it.

Cohort 4 – imlunestrant on BCRP and P-gp activity

Cohort 4 will be an open-label, fixed-sequence design evaluating the effect of imlunestrant on BCRP and P-gp activity. Eligible participants will take part in 2 treatment periods. Participants will be admitted to the CRU on Day -1. All participants will receive:

- **Day 1:** 10 mg rosuvastatin and 0.25 mg digoxin
- **Day 10:** 400 mg imlunestrant + 10 mg rosuvastatin and 0.25 mg digoxin

There will be a washout period of 9 days between doses of 10 mg rosuvastatin and 0.25 mg digoxin. All participants will remain resident in the CRU until discharge on Day 5, attend the CRU as outpatients on each of Days 6 through 8, then will be re-admitted to the CRU on Day 9 until Day 15.

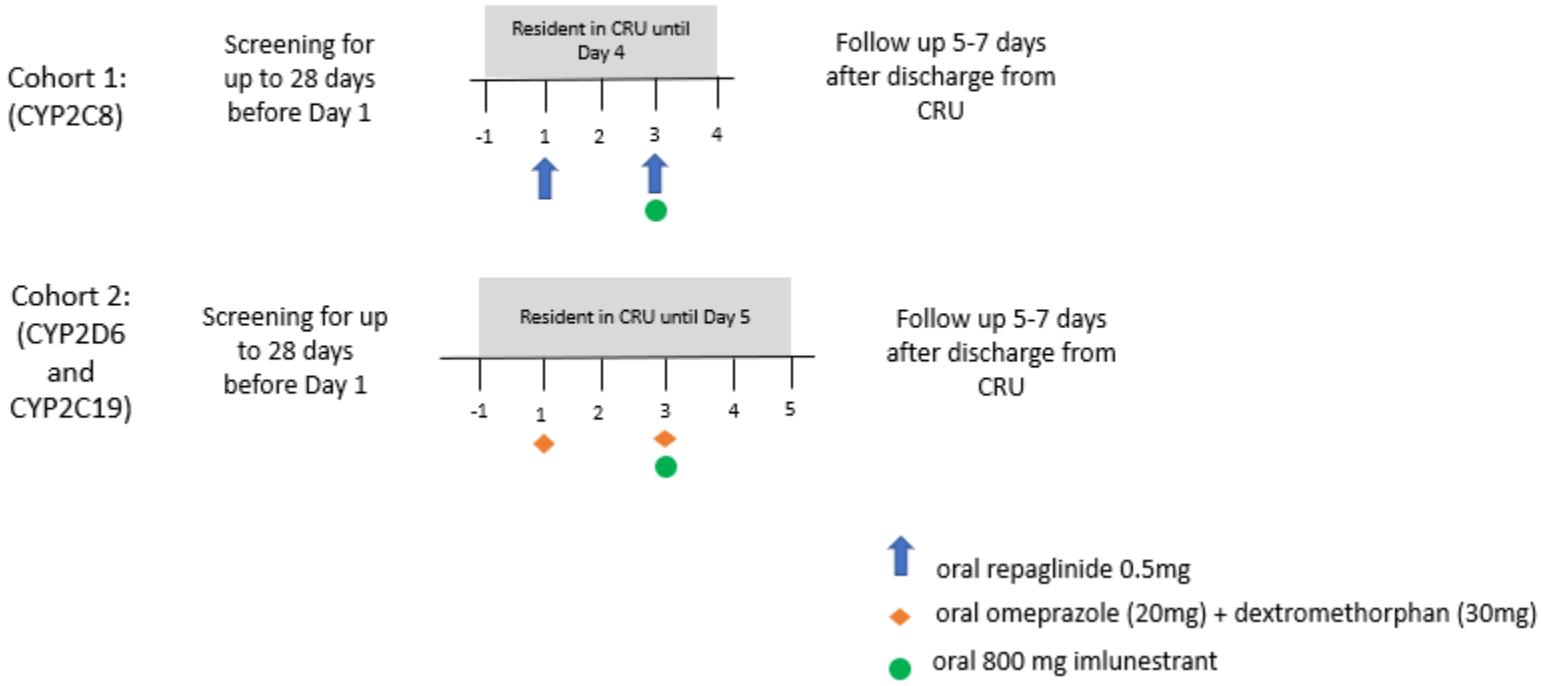
Follow-up

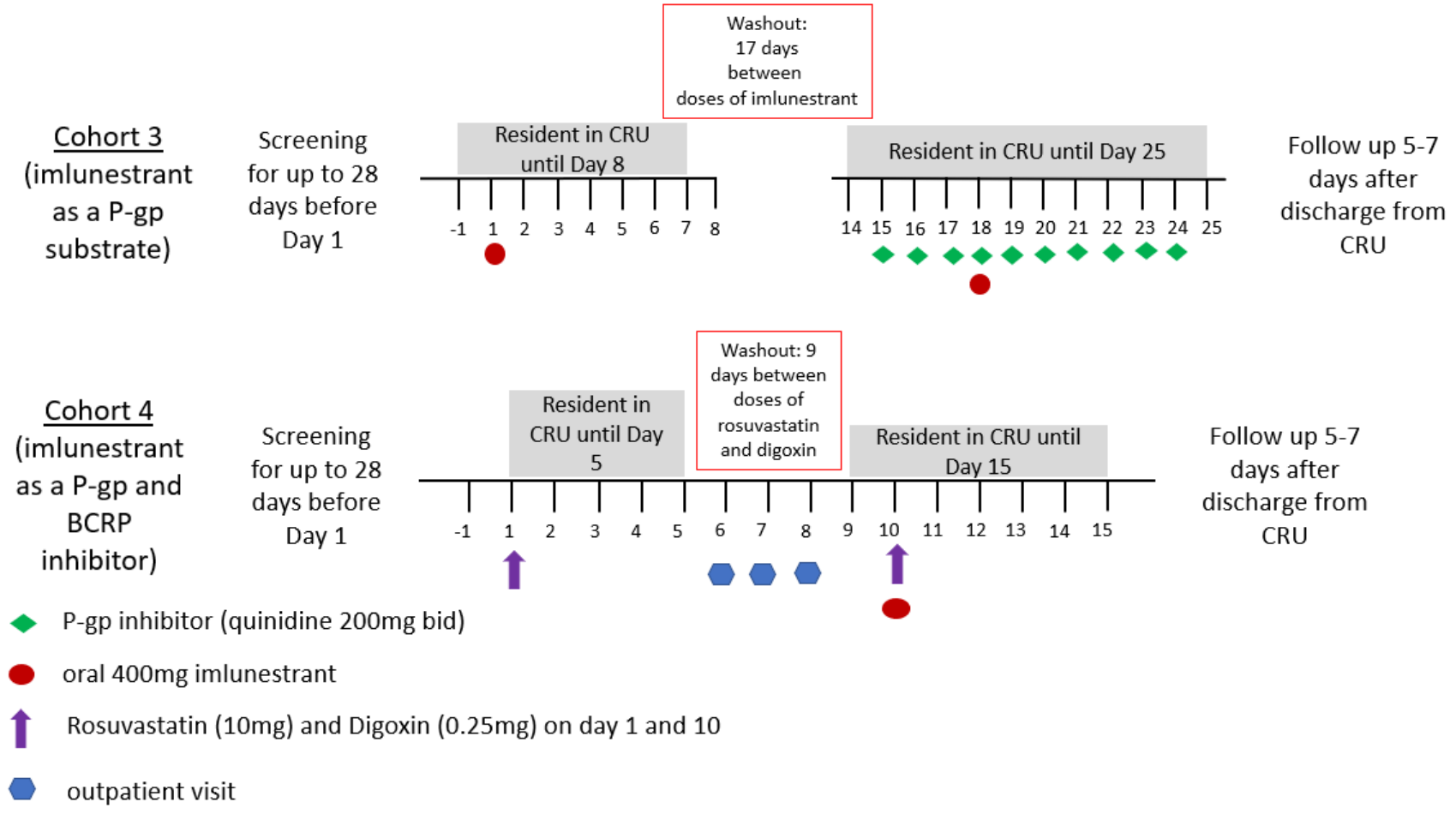
Participants will attend a follow-up visit 5 to 7 days after final discharge from the CRU.

Data Monitoring Committee: No

1.2. Schema

DDI (perpetrator): reversible inhibition to be run in heathy volunteers (WONCBP), study to be run in US





Abbreviations: BCRP = breast cancer resistance protein; BID = twice daily; CRU = clinical research unit; CYP = cytochrome P450; P-gp = P-glycoprotein.

1.3. Schedule of Activities (SoA)

Cohort 1: Effect of Imlunestrant on CYP2C8 Activity

Procedure	Screening (up to 28 days before Day 1)	Treatment period					Follow-up (5-7 days post discharge)	ET	Notes
		-1	1	2	3	4			
Informed consent	X								
Inclusion and exclusion criteria	X								
Demography	X								
Physical examination including height	X	X				X	X	X	Full physical examination will occur at screening, follow-up, and early termination (if applicable). A symptom-directed physical examination will be performed at all other scheduled times and as needed at the discretion of the PI. Height to be measured at screening only.
Weight	X						X	X	
Medical history (includes substance usage [and family history of premature cardiovascular disease])	X								
Past and current medical conditions	X								
FSH test (if applicable)	X								
Urine or breath ethanol test	X	X							
Urine drug screen	X	X							
Human immunodeficiency virus, hepatitis B and C screen	X								

Procedure	**Screening (up to 28 days before Day 1)**	**Treatment period**					**Follow-up (5-7 days post discharge)**	**ET**	**Notes**
		-1	1	2	3	4			
Clinical laboratory tests	X	X				X	X	X	.
12-lead ECG (supine)	X	X			P, 6h		X	X	On Day -1, ECG may be performed any time after check-in. On Day 3, timepoints are relative to imlunestrant dosing time.
Vital signs (supine)	X	X	X	X	X	X	X	X	Timepoints will be defined as follows: Day-1 = Anytime after check-in Day 1 = 2h±1h after repaglinide Day 2 = 24h±4h after repaglinide Day 3 = 4h±1h after imlunestrant Day 4 = prior to discharge
Genetic sample			X						To be collected predose.
Check-in		X							
Discharge from clinic						X			
Outpatient visit							X		
Trial treatment (repaglinide 0.5 mg orally)			X		X				On Day 3, repaglinide will be dosed approximately 2 h after dosing with imlunestrant.
Trial treatment (imlunestrant 800 mg orally)					X				
Plasma PK evaluation of repaglinide			P, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24 h	P, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24h			Sample times are relative to repaglinide dosing times.
Plasma PK evaluation of imlunestrant					P, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24h			Sample times are relative to imlunestrant dosing time.

Procedure	**Screening (up to 28 days before Day 1)**	**Treatment period**					**Follow-up (5-7 days post discharge)**	**ET**	**Notes**
		-1	1	2	3	4			
Blood sample for Coproporphyrin 1			P, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24 h	P, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24h			Sample times are relative to repaglinide dosing times.
Adverse event/Serious adverse event review	X	X	←==========→				X	X	
Concomitant medication review	X	X	←==========→				X	X	

Abbreviations: CYP = cytochrome P450; ECG = electrocardiogram; ET = early termination; FSH = Follicle-stimulating hormone; h = hour(s); P = predose; PI = principal investigator; PK = pharmacokinetic.

Cohort 2: Effect of Imlunestrant on CYP2C19 and CYP2D6 Activity

Procedure	Screening (up to 28 days before Day 1)	Treatment period						Follow-up (5-7 days post discharge)	ET	Notes
		-1	1	2	3	4	5			
Informed consent	X									
Inclusion and exclusion criteria	X									
Demography	X									
Physical examination including height	X	X					X	X	X	Full physical examination will occur at screening, follow-up, and early termination (if applicable). A symptom-directed physical examination will be performed at all other scheduled times and as needed at the discretion of the PI. Height to be measured at screening only.
Weight	X							X	X	
Medical history (includes substance usage [and family history of premature cardiovascular disease])	X									
Past and current medical conditions	X									
Follicle-stimulating hormone test (if applicable)	X									
Urine or breath ethanol test	X	X								
Urine drug screen	X	X								

Procedure	Screening (up to 28 days before Day 1)	Treatment period						Follow-up (5-7 days post discharge)	ET	Notes
		-1	1	2	3	4	5			
Human immunodeficiency virus, hepatitis B and C screen	X									
Clinical laboratory tests	X	X					X	X	X	
12-lead ECG (supine)	X				P, 6h			X	X	
Vital signs (supine)	X	X	X	X	X	X	X	X	X	Timepoints will be defined as follows: Day-1 = Anytime after check-in Day 1 = 2h±1h after omeprazole + dextromethorphan Day 2 = 24 h±4h after omeprazole + dextromethorphan Day 3 = 4h±1h after imlunestrant Day 4 = 24h±4h after imlunestrant Day 5 = prior to discharge
Genetic sample			X							To be collected predose.
Check-in		X								
Discharge from clinic							X			
Outpatient visit								X		
Trial treatment (omeprazole [20 mg] + dextromethorphan [30 mg] orally)			X		X					
Trial treatment (imlunestrant 800mg orally)					X					

Procedure	**Screening (up to 28 days before Day 1)**	**Treatment period**						**Follow-up (5-7 days post discharge)**	**ET**	**Notes**
		-1	1	2	3	4	5			
Plasma PK evaluation of omeprazole, 5-hydroxyomeprazole, dextromethorphan, dextrorphan			P, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24 h	P (48h), 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24h, 36h	48h			
Plasma PK evaluation of imlunestrant					P, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h	24h, 36h	48h			
Adverse event/Serious adverse event review	X	X	←==========→					X	X	
Concomitant medication review	X	X	←==========→					X	X	

Abbreviations: CYP = cytochrome P450; ECG = electrocardiogram; ET = early termination; h = hour(s); P = predose; PI = principal investigator; PK = pharmacokinetic.

Cohort 3: Effect of P-glycoprotein Inhibition on Imlunestrant

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6	7	8	9 to 13 (participant not in CRU at this time)		
Informed consent	X												
Inclusion and exclusion criteria	X												
Demography	X												
Physical examination including height	X	X								X		X	Full physical examination will occur at screening, Day 8, and early termination (if applicable). A symptom-directed physical examination will be performed at all other scheduled times and as needed at the discretion of the PI. Height to be measured at screening only.
Weight	X									X		X	
Medical history (includes substance usage [and family history of premature cardiovascular disease])	X												
Past and current medical conditions	X												

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6	7	8	9 to 13 (participant not in CRU at this time)		
Human immunodeficiency virus, hepatitis B and C screen	X												
Follicle-stimulating hormone test (if applicable)	X												
Urine or breath ethanol test	X	X											
Urine drug screen	X	X											
Clinical laboratory tests	X	X								X		X	Day 8 assessment should be prior to discharge.
Check-in		X											
Discharge from clinic										X			
12-lead ECG (supine)	X		P, 6h							X		X	On Day 1, timepoints are relative to imlunestrant dosing time. Day 8 assessment should be prior to discharge.

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6	7	8	9 to 13 (participant not in CRU at this time)		
Vital signs (supine)	X	X	X	X	X	X	X	X	X	X		X	Timepoints will be as follows: Day-1: Any time after check-in Day 1 = 4h±1h after imlunestrant Day 2 = 24h±4h after imlunestrant Day 3 = 48h±4h after imlunestrant Day 4 = 72h±4h after imlunestrant Day 5 = 96h±4h after imlunestrant Day 6 = 120h±4h after imlunestrant Day 7 = 144h±4h after imlunestrant Day 8 = prior to discharge
Genetic sample			X										To be collected predose.
Trial treatment (imlunestrant 400 mg orally)			X										
Plasma PK evaluation of imlunestrant			P, 1h, 2h, 3h, 4h, 5h,6h, 8h, 12h	24h, 36h	48h	72h	96h	120h	144h	168h			

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6	7	8	9 to 13 (participant not in CRU at this time)	
Adverse event/Serious adverse event review	X	X	←==========→								X	X	On Days 9 to 13, AEs will be reported spontaneously by the participant. Participants will be instructed to call the CRU in the event of an AE.
Concomitant medication review	X	X	←==========→								X	X	On Days 9 to 13, concomitant medications will be reported spontaneously by the participant. If the participant does need to take concomitant medication, they must contact the CRU so that the PI and CP may consult and approve the concomitant medication prior to the participant taking it.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; h = hour(s); P = predose; PI = principal investigator; PK = pharmacokinetic.

Procedure	Treatment Period									Follow-up (5-7 days post discharge)	ET	Notes
	14	15	16	17	18	19	20	21	22-25			
Physical examination										X	X	Full physical examination will occur at follow-up, and early termination (if applicable). A symptom-directed physical examination may be performed as needed at the discretion of the PI.
Weight										X	X	
Clinical laboratory tests	X			X					Day 25 prior to discharge	X	X	
Urine or breath ethanol test	X											
Urine drug screen	X											
Check-in	X											
Discharge from clinic									Day 25			
Outpatient visit										X		
12-lead ECG (supine)	X	X			P, 6h				Day 25 prior to discharge	X	X	On Day 18, timepoints will be relative to imlunestrant dosing time.

Procedure	Treatment Period									Follow-up (5-7 days post discharge)	ET	Notes
	14	15	16	17	18	19	20	21	22-25			
Vital signs (supine)	X	X	X	X	X	X	X	X	X	X	X	Timepoints will be as follows: Day 14 = anytime after check-in Day 15 = 2h±1h after quinidine Day 16 = 2h±1h after quinidine Day 17 = 2h±1h after quinidine Day 18 = 4h±1h after imlunestrant Day 19 = 24h±4h after imlunestrant Day 20 = 48h±4h after imlunestrant Day 21 = 72h±4h after imlunestrant Day 22 = 96h±4h after imlunestrant Day 23 = 120h±4h after imlunestrant Day 24 = 144 h±4h after imlunestrant Day 25 = prior to discharge
Trial treatment (quinidine 200 mg twice daily)		X	X	X	X	X	X	X	Days 22 to 24			
Trial treatment (imlunestrant 400 mg orally)					X							
Plasma PK evaluation of imlunestrant					P, 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h	24h, 36h	48h	72h	96h, 120h, 144h, 168h			

Procedure	Treatment Period									Follow-up (5-7 days post discharge)	ET	Notes
	14	15	16	17	18	19	20	21	22-25			
Blood sample for Coproporphyrin 1					P, 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h	24h						Sample times are relative to imlunestrant dosing times.
Adverse event/Serious adverse event review	X	←==========→								X	X	
Concomitant medication review	X	←==========→								X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; h = hour(s); P = predose; PK = pharmacokinetic.

Cohort 4: Effect of Imlunestrant on Breast Cancer Reactive Protein and P-glycoprotein Activity

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6-8	9	10		
Informed consent	X											
Inclusion and exclusion criteria	X											
Demography	X											
Physical examination including height	X	X								X	X	Full physical examination will occur at screening, Day 10, and early termination. A symptom-directed physical examination will be performed at all other scheduled times and as needed at the discretion of the PI. Height to be measured at screening only.
Weight	X	X								X	X	
Medical history (includes substance usage [and family history of premature cardiovascular disease])	X											
Past and current medical conditions	X											
FSH test (if applicable)	X											
Urine or breath ethanol test	X	X							X			
Urine drug screen	X	X							X			
Human immunodeficiency virus, hepatitis B and C screen	X											

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6-8	9	10		
Clinical laboratory tests	X	X					X		X		X	At screening, Day -1, and at each check-in and discharge from the CRU.
12-lead ECG (supine)	X	X					X		X	P, 6h	X	On Day -1, ECG may be performed any time after check-in On Day 10, timepoints will be relative to imlunestrant dosing time.
Vital signs (supine)	X	X	X	X	X	X	X	X	X	X		Timepoints will be as follows: Day-1 = Any time after check-in Day 1 = 4h±1h after rosuvastatin and digoxin Day 2 = 24h±4h after rosuvastatin and digoxin Day 3 = 48h±4h after rosuvastatin and digoxin Day 4 = 72h±4h after rosuvastatin and digoxin Day 5 = 96h±4h after rosuvastatin and digoxin Day 6 = 120h±4h after rosuvastatin and digoxin Day 7 = 144h±4h after rosuvastatin and digoxin Day 8 = 168±4h after rosuvastatin and digoxin Day 9 = 192±4h after rosuvastatin and digoxin Day 10 = 4h±1h after imlunestrant
Genetic sample			X									To be collected predose.
Check-in		X							X			

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6-8	9	10		
Discharge from clinic							X					
Outpatient visit								X				Participants will attend the CRU on each of Days 6 through 8 for an outpatient visit.
Trial treatment rosuvastatin (10 mg) and digoxin (0.25 mg)			X							X		
Trial treatment (imlunestrant 400 mg orally)										X		
Plasma PK evaluation of rosuvastatin, digoxin			P, 0.5h, 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h	24h, 36h	48h	72h	96h			P, 0.5h, 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h		
Plasma PK evaluation of imlunestrant										P, 0.5h, 1h, 2h, 3h, 4h, 5h,6h, 8h, 12h		
Urinary PK evaluation of digoxin			0 to 12h							0 to 12h		Sample times are relative to digoxin dosing times.

Procedure	Screening (up to 28 days before Day 1)	Treatment period									ET	Notes
		-1	1	2	3	4	5	6-8	9	10		
Blood sample for Coproporphyrin 1										P, 0.5h, 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h		Sample times are relative to imlunestrant dosing times.
Adverse event/Serious adverse event review	X	X	←==========→								X	
Concomitant medication review	X	X	←==========→								X	

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; h = hour(s); P = predose; PI = principal investigator; PK = pharmacokinetic.

Procedure	Treatment period					Follow-up (5-7 days post discharge)	ET	Notes
	11	12	13	14	15			
Physical examination including height						X	X	Full physical examination will occur at follow-up, and early termination (if applicable). A symptom-directed physical examination may be performed as needed at the discretion of the PI.
Weight						X	X	
Clinical laboratory tests					X	X	X	
12-lead ECG (supine)					X	X	X	
Vital signs (supine)	X	X	X	X	X	X	X	Timepoints will be defined as: Day 11 = 24h±4h after imlunestrant Day 12 = 48h±4h after imlunestrant Day 13 = 72h±4h after imlunestrant Day 14 = 96h±4h after imlunestrant Day 15 = 120h±4h after imlunestrant
Discharge from clinic					X			
Outpatient visit						X		
Plasma PK evaluation of rosuvastatin, digoxin	24h, 36h	48h	72h	96h	120h			

Procedure	**Treatment period**					**Follow-up (5-7 days post discharge)**	**ET**	**Notes**
	11	12	13	14	15			
Plasma PK evaluation of imlunestrant	24h, 36h	48h	72h	96h	120h			
Adverse event/Serious adverse event review	←==========→					X	X	
Concomitant medication review	←==========→					X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; h = hour(s); PI = principal investigator; PK = pharmacokinetic.

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 ET and options are often limited to chemotherapy.

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

2.1. Study Rationale

Study J2J-MC-JZLI (JZLI) is a Phase 1 open-label, 4-cohort study of imlunestrant administered to healthy females of non-childbearing potential. In vitro data indicates that imlunestrant has the potential to inhibit CYP2C8, CYP2C19, CYP2D6, P-gp, and BCRP, and clinical studies are required to quantify this potential effect. The FDA guidance on DDIs recommend repaglinide, omeprazole, and dextromethorphan as sensitive probes of CYP2C8, CYP2C19, and CYP2D6, respectively. Similarly, digoxin and rosuvastatin are recommended probes to quantify inhibition of P-gp and BCRP, respectively. Therefore, the purpose of this study is to investigate the effect of imlunestrant on CYP2C8, CYP2C19 and CYP2D6, and P-gp and BCRP activity by use of repaglinide, omeprazole, dextromethorphan, and digoxin and rosuvastatin, respectively. In vitro data also identified imlunestrant as a substrate of P-gp. The FDA recommends quinidine as a relatively selective inhibitor of P-gp when compared to other P-gp inhibitors that target CYP3A4 in addition to P-gp. Therefore to investigate the effect of P-gp inhibition on imlunestrant this study will employ repeat dosing of quinidine to inhibit both intestinal and central P-gp activity (liver, kidney, or both). The results of this study will inform dosing instructions in ongoing patient trials.

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).

SERDs are one of the treatment options for ER+/ HER2- breast cancer patients. Fulvestrant is currently the only regulatory agency-approved SERD for the treatment of ER+ metastatic breast cancer (Nardone et al. 2019). Its efficacy is highly dose dependent, where increasing the administered dose led to improved survival (Di Leo et al. 2014). However, the intramuscular route of fulvestrant administration limits the amount of fulvestrant that can be given to patients. Even though doses higher than 500 mg per month may lead to better ER degradation, the intramuscular administration route limits the amount of fulvestrant that can be given to patients (Nardone et al. 2019). In addition, several studies have shown that with the current maximum feasible dose, fulvestrant treatment is not able to completely degrade ER in patients and can be associated with early progression (van Kruchten et al. 2015). Thus, there is unmet medical need

to develop oral SERDs with higher bioavailability, greater ER targeting, and degradation efficiency (Nardone et al. 2019).

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

2.2.1. Pharmacokinetics of Imlunestrant

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

CCI

2.3. Benefit/Risk Assessment

Imlunestrant is a potent antagonist and degrader of ERα and has demonstrated significant activity in nonclinical 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 2 × single doses of 400 mg imlunestrant (Cohorts 1, 2, and 4), or 2 × single doses of 200 mg imlunestrant (Cohort 3). Study JZLE has 5 healthy female participants that are receiving a single dose of 400 mg imlunestrant (Parts 1 or 2). These studies are still ongoing.

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

As described in the IB, imlunestrant has been evaluated in a comprehensive set of nonclinical safety studies including good laboratory practice repeat-dose studies of approximately 3 months in rats and monkeys. Single doses of imlunestrant have been generally well tolerated in rats and monkeys. The primary toxicity associated with single doses of imlunestrant was gastrointestinal upset, characterized by vomitus in monkeys and abnormal feces in both species. The most significant adverse findings in repeat-dose toxicity studies with imlunestrant to date occur in the female reproductive tract and are attributable to exaggerated pharmacology of imlunestrant at the ER. There have been no adverse non-reproductive findings up to the highest dose tested in monkeys or up to the highest tolerated dose in rats. Imlunestrant has not been associated with cardiovascular, central nervous, or respiratory system toxicities.

The potential risks associated with exposure to imlunestrant in nonclinical toxicity studies include:

- effects on female reproductive organs, including ovarian follicular cysts, cessation of estrous cycling, and atrophy of the epithelium of the uterus, cervix, and vagina
- maternal and embryofetal toxicity (embryo lethality, teratogenicity)
- hematological changes

- decreased lymphoid cellularity in lymphoid organs
- renal effects, such as tubular degeneration
- evidence of phospholipidosis
- gastrointestinal effects, such as abnormal feces and vomiting
- hepatic effects, such as increased liver enzymes lacking morphological correlates
- phototoxicity, based on an in vitro study, and
- chromosomal damage, based on an in vitro study (not observed in the in vivo study), at levels of imlunestrant higher than patients will receive.

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, or other garments that cover the legs, and hats to cover the head if out in direct sunlight, to reduce the possibility of phototoxicity that may result from imlunestrant exposure based on an in vitro phototoxicity study.

Genotoxicity

Imlunestrant was negative for mutagenicity in the Ames assay. It was positive for chromosomal damage in vitro in the presence of metabolic activation at ≥14 µg/mL 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 at systemic C_{max} and AUC over the last 24-hour dosing interval exposures that are approximately 25- to 55-fold higher than clinical exposures at 800 and 400 mg, respectively, based on single dose clinical PK data. 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 or 2 doses 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	
• Cohort 1: Evaluate the effect of imlunestrant on the PK of repaglinide (CYP2C8 substrate) in healthy women of non-childbearing potential.	• Cohort 1: AUC(0-∞), C_{max} of repaglinide administered alone and in the presence of imlunestrant.
• Cohort 2: Evaluate the effect of imlunestrant on the PK of omeprazole (CYP2C19 substrate) and dextromethorphan (CYP2D6 substrate) in healthy women of non-childbearing potential.	• Cohort 2: AUC(0-∞), C_{max} of omeprazole, 5-hydroxyomeprazole, dextromethorphan and dextrorphan administered alone and in the presence of imlunestrant.
• Cohort 3: Evaluate the effect of quinidine (P-gp inhibitor) on the PK of imlunestrant in healthy women of non-childbearing potential.	• Cohort 3: AUC(0-∞), C_{max} of imlunestrant administered alone and in the presence of quinidine.
• Cohort 4: Evaluate the effect of imlunestrant on the PK of rosuvastatin (BCRP substrate) and digoxin (P-gp substrate) in healthy women of non-childbearing potential.	• Cohort 4: AUC(0-∞), C_{max} of rosuvastatin and digoxin administered alone and in the presence of imlunestrant.
Secondary	
• To evaluate the safety and tolerability of 400 and 800 mg imlunestrant in healthy females of non-childbearing potential.	• Incidence and severity of AEs and SAEs.

4. Study Design

4.1. Overall Design

Study JZLI is an open-label, 4-cohort, study comprising 4 fixed-sequence crossover cohorts. Cohorts 1 to 4 are in healthy females of non-childbearing potential to investigate the effect of imlunestrant on the PK of repaglinide (Cohort 1), omeprazole and dextromethorphan (Cohort 2), and rosuvastatin and digoxin (Cohort 4), and to investigate the effect of quinidine on the PK of imlunestrant (Cohort 3). Additionally, the safety and tolerability of imlunestrant will be evaluated when administered as a single 800-mg oral dose in the presence of repaglinide or omeprazole and dextromethorphan, and as a single oral 400-mg dose in the presence of quinidine or rosuvastatin and digoxin.

The schema in Section 1.2 illustrates the study design.

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

4.1.1. Screening

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

4.1.2. Treatment and Assessment Period

Cohort 1 – imlunestrant on CYP2C8 activity

Cohort 1 will be an open-label, fixed-sequence design evaluating the effect of imlunestrant on CYP2C8. Participants will be admitted to the CRU on Day -1. All participants will receive:

- **Day 1:** 0.5 mg repaglinide alone
- **Day 3:** 800 mg imlunestrant + 0.5 mg repaglinide

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

Cohort 2 – imlunestrant on CYP2C19 and CYP2D6 activity

Cohort 2 will be an open-label, fixed-sequence design evaluating the effect of imlunestrant on CYP2C19 and CYP2D6. Participants will be admitted to the CRU on Day -1. All participants will receive:

- **Day 1:** 20 mg omeprazole and 30 mg dextromethorphan
- **Day 3:** 800 mg imlunestrant + 20 mg omeprazole and 30 mg dextromethorphan

There will be a washout period of 2 days between doses of omeprazole and dextromethorphan. All participants will remain resident in the CRU until discharge on Day 5.

Cohort 3 – P-gp inhibition on imlunestrant

Cohort 3 will be an open-label, fixed-sequence design evaluating the effect of P-gp on imlunestrant. Eligible participants will take part in 2 treatment periods. Participants will be admitted to the CRU on Day -1. All participants will receive:

- **Day 1:** 400 mg imlunestrant
- **Days 15 to 17:** 200 mg quinidine twice daily (BID) alone
- **Day 18:** 400 mg imlunestrant + 200 mg quinidine BID
- **Day 19 to Day 24:** 200 mg quinidine BID alone

There will be a washout period of 17 days between doses of imlunestrant. All participants will remain resident in the CRU until discharge on Day 8, then will be re-admitted to the CRU on Day 14 until Day 25.

On Days 9 to 13, participants will not be in the CRU. During this time, AEs and concomitant medications on this day will be reported spontaneously by the participant. If the participant does need to take concomitant medication, they must contact the CRU so that the PI and CP may consult and approve the concomitant medication prior to the participant taking it.

Cohort 4 - imlunestrant on BCRP and P-gp activity

Cohort 4 will be an open-label, fixed-sequence design evaluating the effect of imlunestrant on BCRP and P-gp activity. Eligible participants will take part in 2 treatment periods. Participants will be admitted to the CRU on Day -1. All participants will receive:

- **Day 1:** 10 mg rosuvastatin and 0.25 mg digoxin
- **Day 10:** 400 mg imlunestrant + 10 mg rosuvastatin and 0.25 mg digoxin

There will be a washout period of 9 days between doses of 10 mg rosuvastatin and 0.25 mg digoxin. All participants will remain resident in the CRU until discharge on Day 5, attend the CRU as outpatients on each of Days 6 through 8, then will be re-admitted to the CRU on Day 9 until Day 15.

4.1.3. Follow-up

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

4.2. Scientific Rationale for Study Design

The fixed-sequence, crossover design used in each of Cohorts 1 to 4 is typical for interaction studies where a relatively small number of participants are required, because it allows intraparticipant comparisons and eliminates interparticipant comparisons. In addition, a fixed-sequence design is consistent with FDA guidance.

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

Conducting studies in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications, and avoids non-beneficial drug exposures in cancer patients. Healthy females of non-childbearing potential have been selected as the study population since the pharmacologic mechanism of imlunestrant is to degrade the ER, and effects on the female reproductive organs are expected.

4.3. Justification for Dose

4.3.1. Imlunestrant

The proposed efficacious dose of imlunestrant is 400 mg daily and upon multiple dosing there is approximately a 2-fold accumulation at steady state. Therefore, to evaluate the inhibition of CYP2C8 (repaglinide), CYP2C19 (omeprazole) and CYP2D6 (dextromethorphan), which are expressed only in the liver, a single dose of 800 mg imlunestrant will be used to approximate steady-state plasma concentrations. To evaluate the inhibition of P-gp (digoxin) and BCRP (rosuvastatin), which are expressed in the intestinal wall, a single dose of 400 mg imlunestrant will be used to reproduce expected intestinal concentrations. To evaluate the effect of inhibiting P-gp (quinidine) on imlunestrant exposure we will use a single dose of 400 mg to reproduce expected intestinal concentrations in clinical use.

4.3.2. Repaglinide

The selected dose of 0.5 mg for repaglinide is based on typical doses (0.5 to 4 mg) for this drug and is considered to be high enough to provide sufficient plasma concentrations to achieve the objectives of the study.

4.3.3. Omeprazole and Dextromethorphan

A drug cocktail containing oral doses of 40 mg omeprazole, and 30 mg dextromethorphan has been studied previously (Ishii et al. 2018), with no safety concerns or DDIs between the 2 drugs raised. Therefore, the drug cocktail proposed in the current study, which contains 20 mg omeprazole, and 30 mg dextromethorphan is expected to be safe and well tolerated.

4.3.4. Quinidine

The selected dose of 200 mg BID of quinidine for 10 days is within the therapeutic dose range for this drug.

4.3.5. Rosuvastatin and Digoxin

Rosuvastatin and digoxin are commonly used as probes in DDI studies to detect the interaction involving BCRP and P-gp, respectively, either alone or as a cocktail (FDA 2020; Ishii et al. 2018). Rosuvastatin is commonly administered to adults at an oral dose of 5 to 40 mg QD, with the majority of the clinical DDI or pharmacogenetic studies conducted using a 10- or 20-mg dose (Lee et al. 2015; Crestor Prescribing Information, 2020). The suggested 10-mg dose is as a good clinical probe for both hepatic and intestinal BCRP function (Lee et al. 2015). Digoxin recommended therapeutic concentration ranges from 0.5 to 2.0 ng/mL (LANOXIN [digoxin] package insert). However, digoxin may produce clinical benefits below this range therefore the selected dose of 0.25 mg is anticipated to produce C_{max} values in that range (Ishii et al. 2018), and address the study objectives with minimal risk.

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 examinations, vital signs, clinical laboratory tests, and ECGs. All participants will be women of non-childbearing potential.

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

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

5.1. Inclusion Criteria

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

Age

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

Type of Participant

2. Participants who are overtly healthy as determined by medical assessment including medical history, physical examination, clinical laboratory tests, and vital signs.
3. Participants who have clinical laboratory test results within the normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
4. Participants who have venous access sufficient to allow for blood sampling as per the protocol.

Weight

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

Sex and Contraceptive/Barrier Requirements

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

    See Appendix 4 (Section 10.4) for definitions.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

8. Have known allergies to imlunestrant, related compounds or any components of the formulation, repaglinide, omeprazole, dextromethorphan, quinidine, rosuvastatin, or digoxin, as appropriate, or history of significant atopy.
9. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee).
10. Current or chronic history of liver disease or known hepatic or biliary abnormalities.
11. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator (or designee).
12. Have a clinically significant abnormality of blood pressure, pulse rate, or both, as determined by the investigator.
13. Have a history or presence of cardiovascular (for example, symptomatic bradycardia with resting heart rate of <60 beats per minute), respiratory, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data. Appendectomy, hernia repair, and cholecystectomy are considered as acceptable.
14. History of alcoholism or drug/chemical abuse within 2 years prior to initial check-in to the CRU.
15. Alcohol consumption of > 14 units per week. Number of units = [total volume of drink (mL) x alcohol by volume (%)]/1000.
16. Positive ethanol breath/urine test result or positive urine drug screen at screening or each check-in to the CRU, where applicable.
17. Show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen at screening.
    A positive result for hepatitis B surface antigen or hepatitis C antibody will be confirmed by polymerase chain reaction test to determine active infection.
18. Show evidence of hepatitis C or positive hepatitis C antibody at screening.
19. Have evidence of HIV infection or positive human HIV antibodies at screening.
20. Have donated blood of more than 500 mL within the previous 2 months of study screening.
21. Have any medical conditions, medical history, or are taking any medications which are contraindicated in the omeprazole, repaglinide, dextromethorphan, quinidine, rosuvastatin or digoxin labels, as appropriate.

Prior/Concomitant Therapy

22. 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 first dose, unless deemed acceptable by the investigator (or designee).
23. Use or intend to use any prescription medications/products within 14 days prior to first dose until completion of the follow-up visit, unless deemed acceptable by the investigator (or designee), including but not limited to medications that inhibit or induce CYP2C8, CYP2C19, CYP2D6, P-gp or BCRP.
24. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to initial check-in, unless deemed acceptable by the investigator (or designee).
25. 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).

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

29. Smoke more than 10 cigarettes or use the equivalent tobacco, smoking-cessation products, nicotine-containing products, or e-cigarettes (nicotine and non-nicotine) per day. Participants must be willing to abstain from smoking whilst resident at the CRU.
30. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to initial check-in.
31. Receipt of blood products within 2 months prior to initial check-in.
32. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
33. Participants who, in the opinion of the investigator (or designee), should not participate in this study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

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

Imlunestrant will be dosed in the fasted state; participants will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water and food from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing.

In Cohort 1, repaglinide will be dosed approximately 2 hours after dosing with imlunestrant on Day 3. Approximately 15 minutes after dosing with repaglinide, a light breakfast will be administered. An example of a light breakfast is as follows:

Example 1:

- 1 hard-boiled egg
- 1 small piece of toast with butter
- 1 small apple or banana.

Example 2:

- 1 small bowl of cereal or 1 small bagel with cream cheese
- 1 small apple or banana.

Where applicable in Cohorts 2, 3, and 4, imlunestrant may be dosed at the same time as omeprazole and dextromethorphan, quinidine, or rosuvastatin and digoxin in the fasted state.

With the exception of dosing on Day 3 of Cohort 1 where imlunestrant is coadministered with repaglinide, food is allowed from 2 hours post dosing with imlunestrant. With the exception of the water restrictions described above, 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 until follow-up. In addition, all other citrus fruits and tomato-based products will not be allowed from the time of check-in until discharge from the CRU.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

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

5.3.3. Activity

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

5.3.4. Other

Imlunestrant demonstrated the potential for phototoxicity in an in vitro study. Participants will be advised to use sunscreen and to wear clothing such as long sleeve tops that cover the arms, pants, 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 (for example, laboratory safety tests, vital signs) these may be repeated at the investigator's discretion to confirm eligibility.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable for this study.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Interventions Administered

Table JZLI.1. Study Interventions (IMPs) Administered

ARM Name	Cohorts 1 and 2	Cohort 3 and 4	Cohort 1
Intervention Name	imlunestrant	imlunestrant	repaglinide
Type	drug	drug	drug
Dose Formulation	tablet	tablet	tablet
Unit Dose Strength(s)	200 mg	200 mg	0.5 mg
Dosage Level(s)	800 mg (4 × 200 mg)	400 mg (2 × 200 mg)	0.5 mg
Route of Administration	oral	oral	oral
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.	Provided locally by the trial site.
Packaging and Labeling	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.

ARM Name	Cohort 2	Cohort 2	Cohort 3
Intervention Name	omeprazole	dextromethorphan	quinidine
Dose Formulation	capsule	oral suspension	tablet
Unit Dose Strength(s)	20 mg	---	200 mg
Dosage Level(s)	20 mg	30 mg	200 mg BID
Route of Administration	oral	oral	oral
Sourcing	Provided locally by the trial site.	Provided locally by the trial site.	Provided locally by the trial site.
Packaging and Labeling	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.

Abbreviation: BID = twice daily.

ARM Name	Cohort 4	Cohort 4
Intervention Name	rosuvastatin	digoxin
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	10 mg	0.25 mg
Dosage Level(s)	10 mg	0.25 mg
Route of Administration	oral	oral
Sourcing	Provided locally by the trial site.	Provided locally by the trial site.
Packaging and Labeling	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.

6.1.1. Administration Details

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 2 hours after each dosing occasion, unless clinically indicated or for study procedures.

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

Cohort 1 – imlunestrant on CYP2C8 activity

A single dose of 0.5 mg repaglinide will be administered on Day 1. On Day 3, a single oral dose of 0.5 mg repaglinide will be administered approximately 2 hours after dosing with 800 mg imlunestrant. All doses of repaglinide and imlunestrant will be administered with approximately 240 mL of room temperature water while in a sitting position.

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

Cohort 2 – imlunestrant on CYP2C19 and CYP2D6 activity

A single oral dose of 20 mg omeprazole and 30 mg dextromethorphan will be administered in the morning of Day 1. A single oral dose of 800 mg imlunestrant will be administered in combination with 20 mg omeprazole and 30 mg dextromethorphan on Day 3 (imlunestrant should be dosed first, with omeprazole and dextromethorphan being dosed immediately after). Doses of dextromethorphan will be administered via an oral dosing syringe which will be rinsed with approximately 10 mL of room temperature water two times, with each rinse being

administered. All doses of omeprazole and dextromethorphan will be administered with approximately 240 mL of room temperature water while in a sitting position. No additional water is required when omeprazole and dextromethorphan are dosed in combination with imlunestrant.

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

Cohort 3 – P-gp on imlunestrant

A single oral dose of 400 mg imlunestrant will be administered in the morning of Day 1. Twice daily oral doses of 200 mg quinidine will be administered alone on Days 15 to 17, and on Days 19 to 24, and in combination with 400 mg imlunestrant on Day 18.

All doses of imlunestrant and quinidine will be administered with approximately 240 mL of room temperature water while in a sitting position when dosed alone. No additional water is required when quinidine is dosed in combination with imlunestrant.

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

Cohort 4 – imlunestrant on BCRP and P-gp activity

A single oral dose of 10 mg rosuvastatin and 0.25 mg digoxin will be administered in the morning of Day 1. A single oral dose of 400 mg imlunestrant will be administered in combination with 10 mg rosuvastatin and 0.25 mg digoxin on Day 10. All doses of rosuvastatin and digoxin will be administered with approximately 240 mL of room temperature water while in a sitting position. No additional water is required when rosuvastatin and digoxin are dosed in combination with imlunestrant.

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

6.2. Preparation, Handling, Storage, and Accountability

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Cohorts 1 to 4 will not be randomized.

6.4. Study Intervention Compliance

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

6.5. Dose Modification

Dose modification will not be permitted in this study.

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

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

6.7. Treatment of Overdose

Any dose of imlunestrant greater than 800 mg (Cohorts 1 and 2), or >2 doses of 400 mg (Cohorts 3 and 4) within a 24-hour time period will be considered an overdose.

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

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

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

6.8. Concomitant Therapy

For all participants, any medication or vaccine (including over-the-counter or prescription medicines, vitamins, phytotherapeutic/plant-derived preparations 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. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

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

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

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study to complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, or will remain in the study and follow procedures for remaining study visits, as shown in the SoA (Section 1.3).

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study, or
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons

7.1.1. Liver Chemistry Stopping Criteria

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

- ALT or AST >5× ULN
- ALT or AST >3× ULN and TBL >2× ULN or international normalized ratio >1.5
- ALT or AST >3× ULN and the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
- ALP >3× ULN
- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)

Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Appendix 6 (Section 10.6).

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

- CK elevation of >8 × ULN (or >1600 IU/L)
- lipase and/or amylase ≥3× ULN (Appendix 6; Section 10.6; should be considered by the investigator).

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

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

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if 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.
- The priority of assessments at individual timepoints should be as follows: vital signs > ECGs > PK blood collection (at nominal timepoint) > clinical laboratory assessments.

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

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the 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.
- ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.
- ECGs will be interpreted by a qualified physician (the investigator or qualified designee) as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.
- If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed, and must document his/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 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

- All protocol-required clinical laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA and standard collection requirements.

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

8.2.5. Safety Monitoring

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 6, Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline (except for participants 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 laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computerized tomography scan).

Based on the 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 5 conditions:

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

3. Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN).
    - In participants with baseline ALP ≥1.5 × ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests.
4. Hepatic event considered to be an SAE.

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

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

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

- AEs
- SAEs
- PCs

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE 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	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A

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

* SAEs occurring after participant has completed the study 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.
- In Cohort 1, blood samples of approximately 5 mL will be collected for measurement of concentrations of repaglinide. In Cohort 2, blood samples of 5 mL will be collected for measurement of concentrations of omeprazole, 5-hydroxyomeprazole, dextromethorphan, and dextrorphan. In Cohort 4, blood samples of approximately 5 mL will be collected for the measurement of rosuvastatin, digoxin.
- Urinary samples of approximately 10 mL will be collected to determine the urinary concentrations of digoxin in Cohort 4. Samples will be collected at the time points specified in the SoA (Section 1.3). Up to 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded, as well as the date and time of each imlunestrant, rosuvastatin and digoxin, quinidine, omeprazole and dextromethorphan, and repaglinide 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.

Plasma concentrations of imlunestrant, dextromethorphan, dextrorphan, omeprazole, 5-hydroxyomeprazole, repaglinide, rosuvastatin will be assayed using a validated liquid chromatography mass spectrometry method. The unbound concentration in plasma may also be measured. Urinary digoxin concentration will be assayed using a validated liquid chromatography mass spectrometry method. Plasma coproporphyrin 1 will be assayed using a validated liquid chromatography mass spectrometry method. Samples collected for the analysis of plasma and urine concentrations may be stored and analyzed for future exploratory analysis related to drug disposition.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following last participant visit for the study. During this time,

samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein binding work.

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

Venous blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of Coproporphyrin I in Cohorts 1, 3, and 4, as specified in the SoA (Section 1.3).

8.8. Immunogenicity Assessments

Not applicable for this study.

8.9. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

The primary endpoints will be evaluated to assess any potential DDI between imlunestrant and repaglinide, omeprazole and dextromethorphan, or rosuvastatin and digoxin, and to assess the effect of P-gp inhibition in imlunestrant by use of quinidine.

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 IMP, or if they take the correct treatment.
Safety	All participants who take at least 1 dose of IMP.
Pharmacokinetic Analysis	All participants who received at least 1 dose of IMP and have evaluable PK.

9.2.1. Study Participant Disposition

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

9.2.2. Study Participant Characteristics

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

9.2.3. Treatment Compliance

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

9.3. Statistical Analyses

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

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

Safety analyses will be conducted for all enrolled participants who received at least 1 dose of IMP, whether or not they completed all protocol requirements.

Additional exploratory analyses 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 the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.3.1. Safety Analyses

9.3.1.1. Clinical Evaluation of Safety

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

The number of investigational SAEs will be reported.

9.3.1.2. Statistical Evaluation of Safety

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

9.3.2. Pharmacokinetic Analyses

9.3.2.1. PK Parameter Estimation

PK parameter estimates will be calculated by standard noncompartmental methods. The primary PK parameters for analysis of imlunestrant, repaglinide, omeprazole and 5-hydroxyomeprazole, dextromethorphan and dextrorphan, rosuvastatin and digoxin will be: C_{max}, AUC(0-∞), and t_{max}. The AUC (0-∞) and C_{max} ratio of 5-hydroxyomeprazole to omeprazole and dextrorphan to dextromethorphan will be calculated. Other noncompartmental parameters, such as $t_{1/2}$, apparent total body clearance of drug calculated after extravascular administration, and apparent volume of distribution during the terminal phase after extravascular administration, may be reported as appropriate. Plasma concentrations of Coproporphyrin I in Cohorts 1, 3, and 4 will be summarized by descriptive statistics as appropriate.

In Cohort 4, digoxin renal clearance (CL_r) will be calculated on Days 1 and 10 by dividing the cumulative amount excreted in urine collected for 12 hours by the plasma AUC(0-12).

9.3.2.2. PK Statistical Inference

PK parameters will be evaluated to estimate DDIs in all cohorts. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

To estimate the effect of:

- imlunestrant with repaglinide (Cohort 1),
- imlunestrant with omeprazole and dextromethorphan (Cohort 2),
- quinidine with imlunestrant (Cohort 3), and
- imlunestrant with rosuvastatin and digoxin (Cohort 4).

Log-transformed C_{max} and AUC(0-∞) parameters for repaglinide (Cohort 1), omeprazole and 5-hydroxyomeprazole, dextromethorphan and dextrorphan (Cohort 2), imlunestrant (Cohort 3) and rosuvastatin and digoxin (Cohort 4) will be analyzed using a linear mixed-effects model with a fixed effect for treatment and a random effect for participant.

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

Where appropriate, PK parameters will be summarized using descriptive statistics.

9.3.3. Pharmacodynamic Analyses

Not applicable for this study.

9.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable for this study.

9.4. Interim Analysis

An interim analysis will be conducted after the completion of Cohorts 1 and 2 (that is, after Cohort 2). If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

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 10.1 (Section 10.1.4).

9.5. Sample Size Determination

In Cohorts 1, 2, and 4, approximately 27 participants should be enrolled to ensure that at least 22 evaluable participants in each of these cohorts complete the study. The sample size (N=22) will provide at least 80% power that the 90% CI of the ratio is included in the acceptance interval between 0.8 and 1.25, assuming that the expected geometric mean ratio is 1.05 and the intra-subject CV is 22% for AUC. In Cohort 3, approximately 32 participants should be enrolled to ensure that at least 26 evaluable participants in this cohort completes the study. The sample size (N=26) will provide at least 85% power that the 90% CI of the ratio is included in the acceptance interval between 0.8 and 1.25, assuming that the expected geometric mean ratio is 1.05 and the intra-subject CV is 22% for AUC.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH 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.
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

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

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

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the 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 plans for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone, email, or both) 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.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

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

Data Capture System

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

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

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in 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.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the 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. Current medical records must also be available.
- Definition of what constitutes source data can be found in Section 10.1.4.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

10.1.8. Publication Policy

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.

10.1.9. Investigator Information

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

10.2. Appendix 2: Clinical Laboratory Tests

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

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count	Bicarbonate (total CO_2)
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes	Glucose
Platelets	Creatine kinase
	Gamma-glutamyl transferase
Coagulation	Blood urea nitrogen
Prothrombin time	Direct bilirubin
Activated partial thromboplastin time	Uric acid
International normalized ratio	Total protein
	Albumin
	Total bilirubin
Differential White Blood Cells (Absolute Counts)	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]
Urobilinogen	Hepatitis B core antibody[b]
Blood	Hepatitis C antibody[b,c]
Nitrite	Human immunodeficiency virus antibodies[b]
	Follicle-stimulating hormone (if applicable)[b]

a Performed at screening and each check-in, where appropriate.

b Performed at screening only.

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

10.2.1. Blood Sampling Summaries

These tables summarize the approximate number of venipunctures and blood volumes for all blood sampling during the study.

Protocol J2J-MC-JZLI Sampling Summary – Cohort 1

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	3	33
Pharmacokinetics - imlunestrant[b]	2	10	20
Pharmacokinetics - repaglinide[b]	5	20	100
Coproporphyrin 1	3	20	60
Genetic sample	10	1	10
Total			241.8
Total for clinical purposes			250

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

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

Protocol J2J-MC-JZLI Sampling Summary – Cohort 2

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	3	33
Pharmacokinetics - imlunestrant[b]	2	12	24
Pharmacokinetics – omeprazole, 5-hydroxyomeprazole, dextromethorphan, dextrophan	5	22	110
Genetic sample	10	1	10
Total			195.8
Total for clinical purposes			200

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.

Protocol J2J-MC-JZLI Sampling Summary – Cohort 3

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	6	66
Pharmacokinetics - imlunestrant[b]	2	34	68
Coproporphyrin 1	3	10	30
Genetic sample	10	1	10
Total			192.8
Total for clinical purposes			200

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.

Protocol J2J-MC-JZLI Sampling Summary – Cohort 4

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	5	55
Pharmacokinetics - imlunestrant[b]	2	16	32
Pharmacokinetics – rosuvastatin, digoxin	5	31	155
Coproporphyrin 1	3	10	30
Genetic sample	10	1	10
Total			300.8
Total for clinical purposes			310

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, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected DDI. • 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. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social 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 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 (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to

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

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, 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, evaluations, or both, as medically indicated or as requested by sponsor or designee to elucidate the nature, causality, or both of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via Paper 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 (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman not of Childbearing Potential

Females are considered women not of childbearing potential if:

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

Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, bilateral salpingectomy, 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 postmenopausal state is defined as:

1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or
2. A woman 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: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to imlunestrant or breast/endometrial cancer and related diseases. They may also be used to develop tests/assays including diagnostic tests related to imlunestrant and breast/endometrial cancer. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to imlunestrant or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on imlunestrant continues but no longer than 15 years or other period as per local requirements.

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

See Section 8.2.5.1 for guidance on appropriate test selection.

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: 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-∞)	area under the concentration versus time curve from zero to infinity
BCRP	breast cancer resistance protein
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
CRU	clinical research unit
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction

EC	endometrial cancer
ECG	electrocardiogram
EDC	electronic data capture system
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ER	estrogen receptor
ERα	estrogen receptor α
GCP	good clinical practice
HIV	human immunodeficiency virus
HSA	human serum albumin
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
IEC	independent ethics committee
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 informed consent form.
INR	international normalized ratio
IP	investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board

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. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • 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 • 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.
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
P-gp	P-glycoprotein
PK	pharmacokinetics
QD	once daily
QTc	corrected QT interval
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERD	selective estrogen receptor degrader
SoA	schedule of activities
$t_{1/2}$	half-life associated with the terminal rate constant in non-compartmental analysis
TBL	total bilirubin level
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.
t_{max}	time of maximum observed drug concentration

ULN	upper limit of normal

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