J2J-MC-JZLI Statistical Analysis Plan Version 2

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

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STATISTICAL ANALYSIS PLAN

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

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Clinical Phase I

1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
A_e	Amount of drug excreted
AUC	Area under the concentration versus time curve
AUC(0-12)	Area under the concentration versus time curve from time zero to time 12h
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BCRP	Breast cancer resistance protein
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable drug concentration
CL_R	Renal clearance
C_{max}	Maximum observed drug concentration
C_{min}	Minimum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
F_e	Fraction of dose excreted unchanged
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	Metabolite:parent ratio based on AUC(0-∞)
MR_{Cmax}	Metabolite:parent ratio based on C_{max}
MRE	Magnetic resonance elastography

MW	Molecular weight
P-gp	P-glycoprotein
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 05 April 2022) and Protocol Amendment (a) (final version dated 26 June 2022).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. For open-label studies, this SAP must be signed off prior to first participant visit for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES AND ENDPOINTS

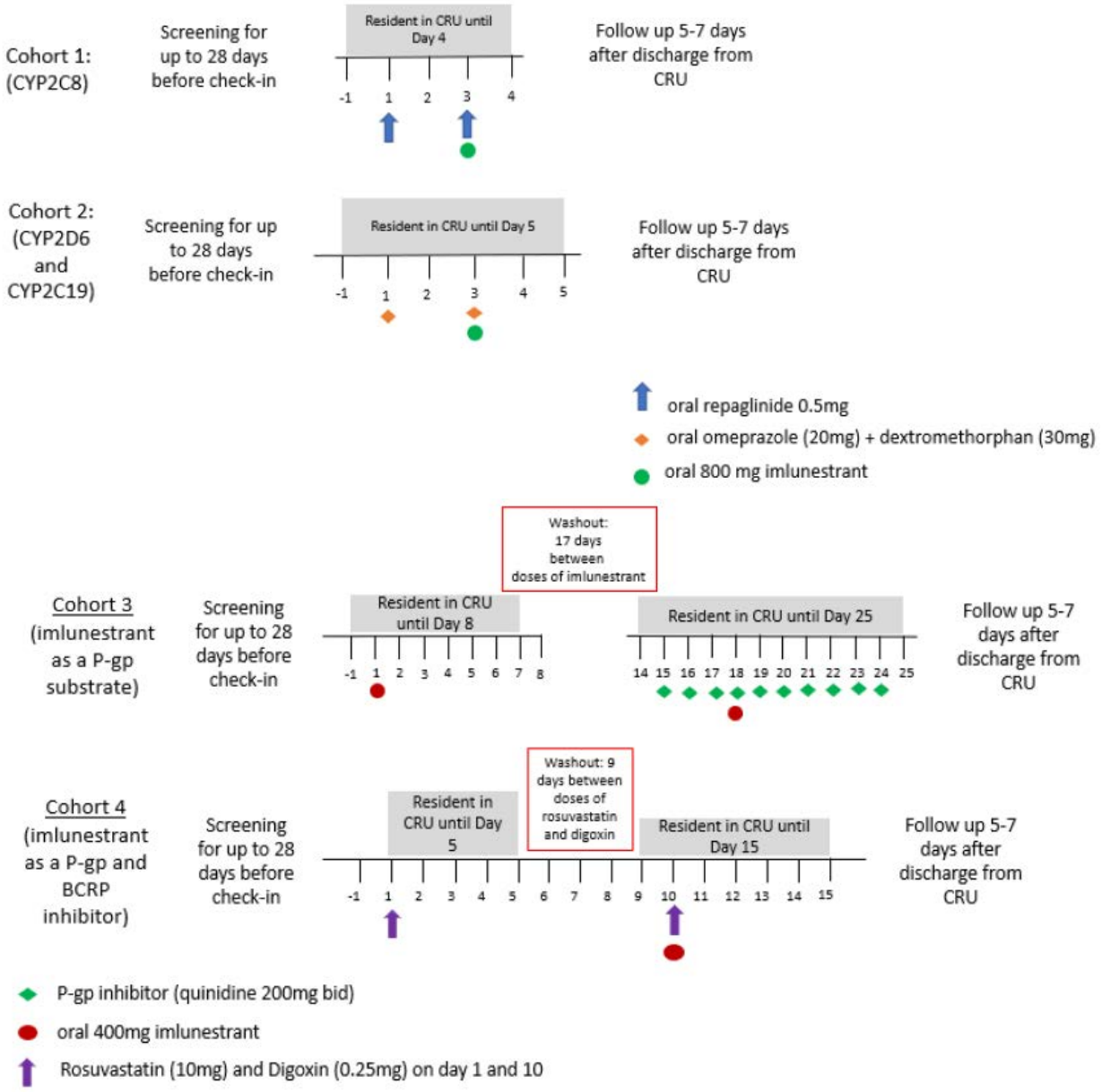
Objectives	Endpoints
Primary	
• Cohort 1: Evaluate the effect of imlunestrant on the PK of repaglinide (CYP2C8 substrate) in healthy women of non-childbearing potential.	• Cohort 1: area under the concentration versus time curve from zero to infinity [AUC(0-∞)], maximum observed drug concentration (C_{max}) of repaglinide administered alone and in the presence of imlunestrant.
• Cohort 2: Evaluate the effect of imlunestrant on the PK of omeprazole (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-glycoprotein [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 (breast cancer resistance protein [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 adverse events (AEs) and serious adverse events (SAEs).

5. STUDY DESIGN

Study J2J-MC-JZLI (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 schemas below illustrate the study design.



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

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

5.1 Screening

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

5.2 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 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

On Days 9 to 13, participants will dose at home. 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 while dosing at home, they must contact the CRU so that the principal investigator and clinical pharmacologist may consult and approve the concomitant medication prior to the participant taking it.

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.

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, then re-admitted to the CRU on Day 9 until Day 15.

5.3 Follow-up

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

6. TREATMENTS

The following is a list of the study treatment sequence names that will be used in the TFLs.

Cohort	Study Treatment Sequence Name	Abbreviation	Treatment order in TFL
1	0.5 mg repaglinide (Day 1) / 800 mg imlunestrant + 0.5 mg repaglinide (Day 3)	Sequence 1	1
2	20 mg omeprazole + 30 mg dextromethorphan (Day 1) / 800 mg imlunestrant + 20 mg omeprazole + 30 mg dextromethorphan (Day 3)	Sequence 2	2
3	400 mg imlunestrant (Day 1) / 200 mg quinidine BID (Days 15 to 17) / 400 mg imlunestrant + 200 mg quinidine BID (Day 18) / 200 mg quinidine BID (Days 19 to 24)	Sequence 3	3
4	10 mg rosuvastatin + 0.25 mg digoxin (Day 1) / 400 mg imlunestrant + 10 mg rosuvastatin + 0.25 mg digoxin (Day 10)	Sequence 4	4

BID = twice daily

The following is a list of the study treatment names that will be used in the TFLs.

Cohort	Study Treatment Name	Treatment order in TFL
1	0.5 mg repaglinide	1
	800 mg imlunestrant + 0.5 mg repaglinide	2
2	20 mg omeprazole + 30 mg dextromethorphan	3
	800 mg imlunestrant + 20 mg omeprazole + 30 mg dextromethorphan	4
3	400 mg imlunestrant (Day 1)	5
	200 mg quinidine BID (Days 15 to 17)	6
	400 mg imlunestrant + 200 mg quinidine BID (Day 18)	7
	200 mg quinidine BID (Days 19 to 24)	8
4	10 mg rosuvastatin + 0.25 mg digoxin	9
	400 mg imlunestrant + 10 mg rosuvastatin + 0.25 mg digoxin	10

BID = twice daily

7. SAMPLE SIZE JUSTIFICATION

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. CCI [redacted] In Cohort 3, approximately 32 participants should be enrolled to ensure that at least 26 evaluable participants in this cohort completes the study. CCI [redacted]

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all participants who received at least one dose of study drug and have at least one postdose safety assessment.

The "Pharmacokinetic" population will consist of all participants who received at least one dose of study drug and have evaluable PK data. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, min, max and n; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 8.1.1 or later).

Plasma concentrations of imlunestrant (LY3484356), repaglinide, omeprazole and 5-hydroxyomeprazole, dextromethorphan and dextrorphan, rosuvastatin and digoxin will be used determine the following PK parameters, where possible:

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-12)	ng.h/mL	area under the concentration versus time curve from time zero to time 12h (digoxin only)
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (imlunestrant, repaglinide, omeprazole, dextromethorphan, rosuvastatin and digoxin only)
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (imlunestrant, repaglinide, omeprazole, dextromethorphan, rosuvastatin and digoxin only)
MR_{AUC}		metabolite:parent ratio based on AUC(0-∞) (5-hydroxyomeprazole/omeprazole and dextrorphan/dextromethorphan only)
MR_{Cmax}		metabolite:parent ratio based on C_{max} (5-hydroxyomeprazole/omeprazole and dextrorphan/dextromethorphan only)

Urine concentrations of digoxin will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
$A_e(0\text{-}12)$	mg	amount of drug excreted unchanged between time zero and 12 hours post-dose
$F_e(0\text{-}12)$	%	fraction of dose excreted unchanged between time zero and 12 hours post-dose
CL_R	L/h	renal clearance

Plasma concentrations of coproporphyrin 1 will be used determine the following PK parameters, where possible:

Parameter	Units	Definition
$AUC(0\text{-}t_{last})$	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-12)	ng.h/mL	area under the concentration versus time curve from time zero to time 12h (cohort 1 only)
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration

The metabolite:parent ratios (MR_{AUC} and MR_{Cmax}) will be calculated as follows:

MR_{AUC} = ($AUC_{0\text{-}\infty}$ metabolite / MW metabolite) / ($AUC_{0\text{-}\infty}$ parent / MW parent), where MW is the molecular weight of each analyte.

If for any reason the $AUC(0\text{-}\infty)$ is not calculable then an alternative AUC such as $AUC(0\text{-}t_{last})$ may be used.

MR_{Cmax} = (C_{max} metabolite / MW metabolite) / (C_{max} parent / MW parent), where MW is the molecular weight of each analyte.

The molecular weights of parents and metabolites to be used in the adjustment are as follows:

Parent	MW* (g/mol)	Metabolites	MW* (g/mol)
omeprazole	345.4	5-hydroxyomeprazole	361.4
dextromethorphan	271.4	dextrorphan	257.37

Abbreviation: MW = Molecular weight.
* Molecular weights obtained from PubChem

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).

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final CSR.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{1/2}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK Parameters with the exception of special handling of certain concentrations reported below the quantifiable lower limit of the assay (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

  - The compound is non-endogenous.
  - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.
  - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.
- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.
- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be the minimum observed drug concentration (C_{min}) for the dosing interval.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final CSR.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window of ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final CSR.

Treatment of Outliers during PK Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.
- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data

remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

PK parameters will be evaluated to estimate drug-drug interactions (DDIs) in all cohorts. The treatment differences will be back-transformed to present the ratios of geometric least squares 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 analysed separately using a linear mixed-effects model with a fixed effect for treatment and a random effect for participant. The geometric least square means for each treatment, geometric least square mean ratios and the corresponding 90% CI will be presented.

The t_{max} will be analyzed using a non-parametric method. Estimates of the median difference (based on individual paired differences) corresponding 90% CIs, and p-values from the Wilcoxon signed rank test will be calculated for the same comparisons.

For coproporphyrin 1, log-transformed AUC(0-t_{last}) and AUC(0-12) parameters will be analysed using a linear mixed-effects model with a fixed effect for treatment and a random effect for participant. The geometric least square means for each treatment, geometric least square mean ratios and the corresponding 90% CI will be presented. The SAS code will be similar to that above. The following comparisons will be made:

- Imlunestrant + repaglinide (test, Cohort 1, AUC[0-t_{last}]) versus repaglinide alone (reference, Cohort 1, AUC[0-t_{last}])
- Quinidine with imlunestrant (test, Cohort 3, AUC[0-t_{last}]) versus repaglinide alone (reference, Cohort 1, AUC[0-t_{last}])
- Imlunestrant with rosuvastatin and digoxin (test, cohort 4, AUC[0-t_{last}]) versus repaglinide alone (reference, Cohort 1, AUC[0-12])

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE (TEAE) is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. The TEAEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2022). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter, cohort, and treatment sequence, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment sequence together with changes from baseline, where baseline is defined as the Day -1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by cohort.

Values for individual participants will be listed.

9.4.5 Electrocardiograms

Electrocardiograms (ECGs) will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

9.4.6 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.5.1 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Use of acetaminophen during the study, which has potential for hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

9.4.7 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

9.4.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

An interim analysis will be conducted after the completion of Cohorts 1 and 2 (that is, after Cohort 2). Log-transformed C_{max} and AUC(0-∞) parameters will be evaluated to estimate DDIs in Cohorts 1 and 2. The analysis will be similar to that described in Section 9.3.2 and will estimate the effect of:

- imlunestrant with repaglinide (Cohort 1),
- imlunestrant with omeprazole and dextromethorphan (Cohort 2).

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Coproporphyrin 1 statistical analysis has been added. This change was made after final database lock.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	28 March 2023	Added coproporphyrin 1 statistical analysis

NA = not applicable

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