Statistical Analysis Plan J2J-MC-JZLG (4.0)

Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment

NCT05440344

Approval Date: 02-Jan-2024

STATISTICAL ANALYSIS PLAN

Pharmacokinetics of Imlunestrant in Participants with Hepatic Impairment

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Version: 4.0
Statistical Analysis Plan Date: 21 December 2023

Investigational Medicinal Product: Imlunestrant (LY3484356)

Protocol Reference: J2J-MC-JZLG
Fortrea Study: 8484214

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]).

AE	Adverse event
ANCOVA	Analysis of covariance model
AUC	Area under the concentration versus time curve
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
BMI	Body mass index
BQL	Below the lower limit of quantitation
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last predicted observed drug concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
INR	International normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation

$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
V_{ss}/F	Apparent volume of distribution at steady state after extravascular administration
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 07 January 2022), Protocol Amendment (a) (final version dated 02 March 2022), Protocol Amendment (b) (final version dated 30 June 2022), and Protocol Amendment (c) (final version dated 18 September 2022), and Protocol Amendment (d) (final version dated 18 December 2023).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) 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	
To evaluate the pharmacokinetics (PK) of imlunestrant in women of non-childbearing potential with hepatic impairment compared to control women of non-childbearing potential with normal hepatic function.	Plasma concentration data (total) should be analyzed to estimate measures or parameters describing the PK of imlunestrant (e.g., Area under the concentration versus time curve (AUC), maximum observed drug concentration [C_{max}]) after a single CCI (or lower) imlunestrant dose.
Secondary	
To evaluate the tolerability of imlunestrant in women of non-childbearing potential with hepatic impairment and control women of non-childbearing potential with normal hepatic function.	Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

5. STUDY DESIGN

Study J2J-MC-JZLG (JZLG) is an open-label, single-dose study.

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

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

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

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

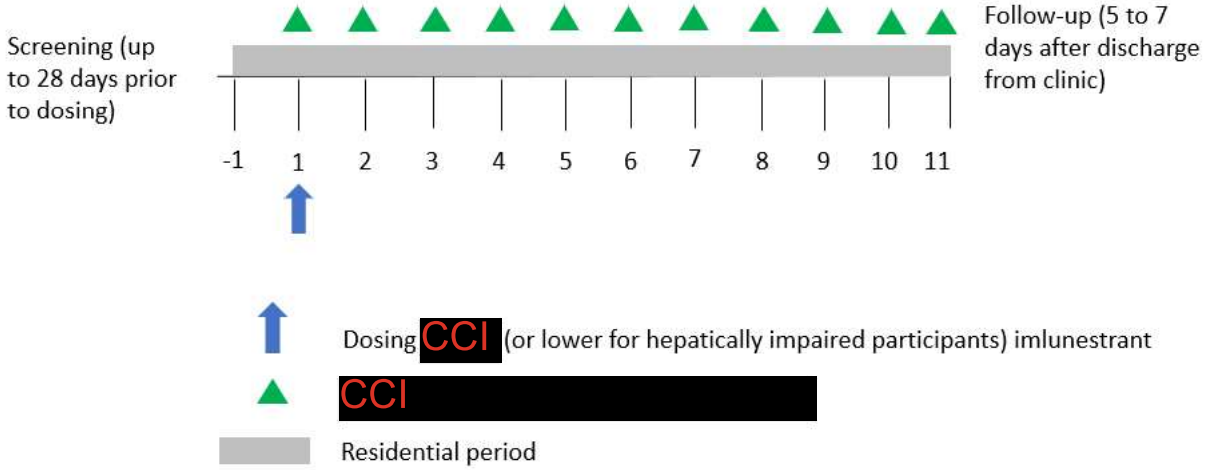
Parameter	1 Point	2 Points	3 Points
Serum alumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Prolonged prothrombin time (sec) or Prothrombin time INR (ratio)	<4 <1.70	4 to 6 1.70 to 2.30	>6 >2.30
Ascites[a]	Absent	Slight Or Subject on 1 medication to control ascites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

Child-Pugh System of Hepatic Impairment: Adapted from Child and Turcotte, 1964, Pugh et al, 1973.
Child-Pugh A: 5 or 6 points; Child-Pugh B: 7 to 9 points; Child-Pugh C: 10 to 15 points (scores are the sum of the 5 parameters).
Abbreviations: INR = international normalized ratio (subject prothrombin time/normal plasma pool prothrombin time).

[a] Ascites is graded according to the following criteria:
Absent: No ascites detectable by manual investigation.
Slight: Ascites palpation doubtful.
Moderate: Ascites detectable by palpation.
Severe: Necessity of paracentesis does not respond to medication treatment.

[b] State of hepatic encephalopathy is graded according to investigator assessment used at the site.

The schema below illustrates the study design.



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

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

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

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

5.1 Screening

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

5.2 Treatment and Assessment Period

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

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

5.3 Follow-up

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

6. TREATMENT

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

Study Treatment Name	Impairment Group	Treatment order in TFL
CCI imlunestrant*	Normal hepatic function	1
	Mild hepatic impairment	2
	Moderate hepatic impairment	3
CCI imlunestrant**	Severe hepatic impairment	4

*CCI tablet (oral)
**CCI tablet (oral)

7. SAMPLE SIZE JUSTIFICATION

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

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

The number of participants in Groups 2 and 3 may be adjusted based on recruitment of participants with severe hepatic impairment. Up to 9 completers may be included in Groups 2 and 3.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Safety” population will consist of all participants who received at least one dose of imlunestrant.

The “Pharmacokinetic” population will consist of all participants who received at least one dose of imlunestrant and have evaluable PK data. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an adverse event (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 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, including Child-Pugh points will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Non compartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.3.5 or later) to the plasma concentrations of total imlunestrant (LY3484356) will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
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-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
C_{max}	ng/mL	maximum observed drug concentration
DN-AUC(0-t_{last})	ng.h/mL/mg	dose normalized area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
DN-AUC(0-∞)	ng.h/mL/mg	dose normalized area under the concentration versus time curve from time zero to infinity
DN-C_{max}	ng/mL/mg	dose normalized 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
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration

The mean fraction unbound value (fu) for imlunestrant determined for each participant will be used to calculate the unbound AUC(0-∞), AUC(0-t_{last}), and C_{max}.

Parameter	Units	Definition
AUC(0-t_{last}),u	ng.h/mL	unbound AUC(0-t_{last}), calculated as AUC(0-t_{last}) * fu
AUC(0-∞),u	ng.h/mL	unbound AUC(0-∞), calculated as AUC(0-∞) * fu
$C_{max,u}$	ng/mL	unbound C_{max}, calculated as C_{max} * fu
CL/F,u	L/h	unbound CL/F, calculated as dose/AUC(0-∞),u

Other noncompartmental unbound parameters such as unbound dose normalized AUC, unbound dose normalized C_{max} and unbound apparent volume of distribution may be reported.

The impact of hepatic impairment on plasma protein binding of imlunestrant will be summarized using descriptive statistics of plasma protein binding data.

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 non-bolus 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}.

- The $t_{1/2}$ 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 last predicted observed 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 lower limit of quantitation (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.

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 specified in the protocol or ± 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 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 analysed with and without the atypical value, and both sets of results will be reported.
2. If n≥6, 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 ≥ 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 CSR. Approval of the final CSR will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

Statistical analysis will be conducted to evaluate the log-transformed PK parameters AUC[0-t_{last}], AUC[0-∞], and C_{max} using an analysis of covariance (ANCOVA) model with hepatic function group as fixed effect and body weight as a covariate. The geometric least square means for each group, geometric least squares mean ratios between each hepatic impairment level versus the control group, and the corresponding 90% confidence intervals (CIs) will be estimated from the ANCOVA model.

The same analysis will also be conducted using dose-normalized PK parameters (DN-AUC[0-t_{last}], DN-AUC[0-∞], and DN-C_{max}), and the unbound PK parameters and dose normalized unbound PK parameters (AUC[0-t_{last}],u, AUC[0-∞],u, and $C_{max,,u}$).

As the severe hepatic impairment group is based on a lower dose, the analysis including severe group may be based on dose-normalized PK parameters only.

The relationship between the PK parameters and Child-Pugh classification parameters (Child-Pugh score, serum albumin concentration, total bilirubin concentration, and prothrombin time) will also be assessed graphically. When assessing Child-Pugh score, the control group will be kept in the analysis (with Child-Pugh score set to 0). The PK parameters AUC(0-∞), C_{max}, and CL/F will be plotted against each Child-Pugh classification parameter separately. There will be two sets of graphs – the first with normal, mild, and moderate groups will assess AUC(0-∞), C_{max}, and CL/F, and the second with normal, mild, moderate, and severe groups will assess DN-AUC(0-∞), DN-C_{max}, and CL/F. A regression line and corresponding 90% CI from a simple linear model will be plotted, if appropriate. As severe group is based on a lower dose, the plots including severe group may be based on dose-normalized PK parameters only.

An exploratory analysis of the PK parameters with National Cancer Institute (NCI) Organ Dysfunction Working Group classification of hepatic dysfunction, in addition to Child-Pugh scoring, will be conducted. This will be the same as the primary analysis except that the group variable will be based on the NCI classification. A simple linear model will also be fitted with the PK parameters as the response versus the NCI classification.

The NCI classifications are presented below:

Group	Group A	Group B	Group C	Group D	Group E
Liver Function	Normal	Mild	Moderate	Severe	Liver Transplant
Total Bilirubin	≤ ULN	B1: ≤ ULN B2: > 1.0x – 1.5x ULN	> 1.5x – 3x ULN	> 3x ULN	Any
SGOT/AST	≤ ULN	B1: > ULN B2: Any	Any	Any	Any

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 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. TEAEs will be summarized by impairment group, 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 impairment group, Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 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 (SAEs) 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 SEPTEMBER 2020). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and impairment group, together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Clinical chemistry, hematology, and 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 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 impairment group.

Values for individual participants will be listed.

9.4.5 Electrocardiogram (ECG)

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, 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 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

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

A review (not an interim analysis) to assess imlunestrant safety and PK will be conducted after at least 3 participants with mild hepatic impairment have completed all PK sampling; imlunestrant will not be administered to participants with moderate hepatic impairment until the review has been completed.

CCI [redacted] imlunestrant will not be administered to participants with severe hepatic impairment until this analysis and review have been completed.

Additional reviews to assess imlunestrant safety and PK will be conducted after 3 participants with severe hepatic impairment have completed all PK sampling, and again after all cohorts have completed all PK samples.

CCI [redacted]

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Following the planned interim analysis, protocol amendment (d) and SAP V4.0 were produced simultaneously to update the originally planned paired t-test to ANCOVA. During the planned interim review of data, the planned paired t-test was deemed inappropriate for the analysis. ANCOVA was proposed to replace paired t-test to adjust for baseline covariates, and graphical assessment of the relationship between PK and Child-Pugh classification parameters will also be performed. This analysis is detailed in Section 9.3.2.

An exploratory analysis of the PK parameters with National Cancer Institute (NCI) Organ Dysfunction Working Group classification of hepatic dysfunction, in addition to Child-Pugh scoring, will be conducted. This analysis is detailed in Section 9.3.2.

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.

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

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

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
Version 1.0	NA	NA; the first version.
Version 2.0	21 October 2022	Updated for protocol amendment (a), (b), and (c)
Version 3.0	03 April 2023	Updated to add dose-normalized and unbound PK analysis
Version 4.0	18 December 2023	Replaced paired t-test with details of ANCOVA analysis method and graphical assessment of the relationship between PK and Child-Pugh classification parameters. Added exploratory statistical analysis of the PK parameters with NCI classification.

NA = not applicable

Signature Page for VV-CLIN-127762 v1.0

Approval	PPD 22-Dec-2023 14:45:17 GMT+0000

Approval	PPD 22-Dec-2023 17:20:42 GMT+0000

Approval	PPD 02-Jan-2024 08:12:32 GMT+0000

Approval	PPD 02-Jan-2024 15:34:30 GMT+0000

Signature Page for VV-CLIN-127762 v1.0