J2J-MC-JZLK Statistical Analysis Plan Version 1.0

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

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STATISTICAL ANALYSIS PLAN

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

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Clinical Phase I

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2. ABBREVIATIONS

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

%AUC(t_{last}-∞)	Percentage of AcUC(0-∞) that is due to extrapolation from the last measurable concentration to infinity
AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-24),ss	Area under the concentration versus time curve from time zero to 24 hours postdose at steady state
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-∞),ss	Area under the concentration versus time curve from time zero to 24 hours postdose at steady state
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
BQL	Below the lower limit of quantitation
CI	Confidence interval
MR(AUC)	Metabolite ratio based upon AUC(0-∞) (metabolite only)
MR(C_{max})	Metabolite ratio based upon C_{max} (metabolite only)
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration (midazolam only)
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration (midazolam only)
C_{max}	Maximum observed drug concentration
$C_{max,ss}$	Maximum observed drug concentration at steady state
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of variation
DDI	Drug-drug interaction
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
$t_{max,ss}$	Time of maximum observed drug concentration at steady state
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 07 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. This SAP must be finalized prior to first participant visit. 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 effect of multiple doses of imlunestrant on the PK of midazolam (CYP3A4 substrate) in healthy women of non-childbearing potential.	• Area under the concentration versus time curve from time zero to infinity [AUC(0-∞)] and maximum observed drug concentration [C_{max}] of midazolam when administered alone and in the presence of imlunestrant.
Secondary	
• To evaluate the effect of multiple doses of imlunestrant on the PK of 1'-hydroxymidazolam (a metabolite of midazolam) in healthy women of non-childbearing potential.	• AUC(0-∞) and C_{max} of 1'-hydroxymidazolam when midazolam is administered alone and in the presence of imlunestrant.
• To evaluate the safety and tolerability of 400 mg imlunestrant once daily (QD) for	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs).

7 days in healthy women of non-childbearing potential.	
• Evaluate the PK of imlunestrant in healthy women of non-childbearing potential.	• Area under the concentration versus time curve from time zero to 24 hours postdose at steady state [$AUC(0\text{-}24)_{,ss}$] and maximum observed drug concentration at steady state ($C_{max,ss}$) of imlunestrant.

5. STUDY DESIGN

Study J2J-MC-JZLK (JZLK) is an open-label, fixed sequence, crossover study to investigate the effect of imlunestrant on the PK of midazolam and its metabolite 1'-hydroxymidazolam in healthy women of non-childbearing potential. Additionally, the PK, safety, and tolerability of imlunestrant will also be evaluated.

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

Screening

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

Treatment and Assessment Period

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

CCI

There will be a washout period of 8 days between doses of midazolam.

Follow-up

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

6. BLINDING

This is a non-randomized, open-label study.

7. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs. In AE outputs, treatment labels will also contain "(Day X)" information.

CCI	Treatment order in TFL
	1
	2
	3

8. SAMPLE SIZE JUSTIFICATION

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

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

9. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all participants who received at least one dose of imlunestrant or midazolam.

The "Pharmacokinetic" population will consist of all participants who received at least one dose of imlunestrant or midazolam 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.

10. STATISTICAL METHODOLOGY

10.1 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, minimum, maximum and number of observations; 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.

For change from baseline summary statistics, each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at that time point. The individual participants' change from baseline values will be used to calculate the summary statistics (arithmetic mean, arithmetic SD, median, minimum, maximum and number of observations) using a SAS procedure such as Proc Univariate.

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

10.2 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.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

The PK parameters will be determined using non-compartmental methods applied with a validated software program (WinNonlin Phoenix Version 8.1.1 or later).

Pharmacokinetics of Imlunestrant

Following oral administration of imlunestrant, plasma concentrations of imlunestrant 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(0-24),ss	ng.h/mL	Area under the concentration versus time curve from time zero to 24 hours postdose
$C_{max,ss}$	ng/mL	Maximum observed drug concentration
$t_{max,ss}$	h	Time of maximum observed drug concentration

Pharmacokinetics of Midazolam and 1'-hydroxymidazolam Metabolite

Following oral administration of midazolam (alone or with imlunestrant), plasma concentrations of midazolam and 1'-hydroxymidazolam will be used to 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(t_{last}-∞)	%	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
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 (midazolam only)
V_z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration (midazolam only)
MR(AUC0-∞)	NA	Metabolite ratio calculated for parameter AUC(0-∞) of metabolite / parent drug
MR(AUC0-t_{last})	NA	Metabolite ratio calculated for parameter AUC(0-t_{last}) of metabolite / parent drug
MR (C_{max})	NA	Metabolite ratio calculated for parameter C_{max} of metabolite / parent drug

NA: Not applicable

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. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- 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 quantitation, with at least one of these concentrations following C_{max}.

- 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 subject 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 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 subject 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 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 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 study report.

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 CSR. Approval of the final CSR will connote approval of the exclusion.

10.3.2 Pharmacokinetic Statistical Methodology

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

To estimate the effect of the DDI of imlunestrant with midazolam, log-transformed C_{max} and AUC(0-∞) of midazolam will be analyzed using a linear mixed-effects model with a fixed effect for treatment and a random effect for participant.

Example SAS code

```
proc mixed data=xxx;
by parameter;
class treatment participant;
model log_pk = treatment / ddfm=kr2 residual cl alpha=0.1;
random participant;
lsmeans treatment / pdiff cl alpha=0.1;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

The t_{max} will be analyzed non-parametrically 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 signed rank test will be calculated.

Example SAS code

```
proc univariate data=xxx cipctldf(alpha = 0.1);
var ref test diff;
ods output quantiles = quant01;
ods output testsforlocation = out01;
run;
```

Where appropriate, midazolam, 1'-hydroxymidazolam, and imlunestrant PK parameters will be summarized using descriptive statistics.

10.4 Safety and Tolerability Assessments

10.4.1 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. 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 SAEs will be listed.

Discontinuations due to AEs will be listed.

10.4.2 Concomitant medication

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

10.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by time point, and listed. Changes from baseline (Day 1 predose) will be included. 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.

10.4.4 Vital signs

Vital signs data will be summarized by time point together with changes from baseline (Day 1 predose). Figures of mean vital signs and mean changes from baseline profiles will be presented by timepoint.

Values for individual participants will be listed.

10.4.5 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.

10.4.6 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 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.

10.4.7 Other assessments

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

10.4.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

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

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. 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.

14. DATA PRESENTATION

14.1 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. Number of observations 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.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 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.”

15. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable

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