Statistical Analysis Plan Version 2 J3D-MC-FNAA

A Phase 1, Randomized, Participant- and Investigator-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose, Drug-Drug Interaction and Food Effect Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3509754 in Healthy Non-Japanese and Japanese Participants

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STATISTICAL ANALYSIS PLAN

A Phase 1, Randomized, Participant-and Investigator-Blind, Placebo-Controlled, Single -and Multiple-Ascending Dose, Drug-Drug Interaction and Food Effect Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3509754 in Healthy Non-Japanese and Japanese Participants

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Clinical Phase I

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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
Ae	Amount of drug excreted
ANOVA	Analysis of variance
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-24)	Area under the concentration versus time curve from time zero to 24 hours postdose
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
AUCτ	Area under the concentration versus time curve during the dosing interval (τ = 24 hours)
BQL	Below the lower limit of quantification
C_{max}	Maximum observed drug concentration
$C_{predose}$	Predose observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular Administration
CL_R	Renal clearance
COVID-19	Coronavirus Disease 2019
CRU	Clinical Research Unit
CSR	Clinical Study Report
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
ECG	Electrocardiogram
Fe	Fraction of dose excreted unchanged
HR	Heart rate
ICH	International Conference on Harmonisation
IL-17	Interleukin-17
IL-19	Interleukin-19

LS	Least squares
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
QD	Once daily
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
R_A(AUC)	Accumulation ratio based upon AUCτ
SAD	Single ascending dose
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_{last}	Time of last observed drug concentration
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular 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 04 September 2020) and Protocol Amendment (d) (final version dated 18 June 2021, only applicable if United Kingdom sites are used).

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. 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

4.1 Primary Objective

The primary objective of the study is to assess the safety and tolerability following single or multiple doses of LY3509754 administered to healthy participants.

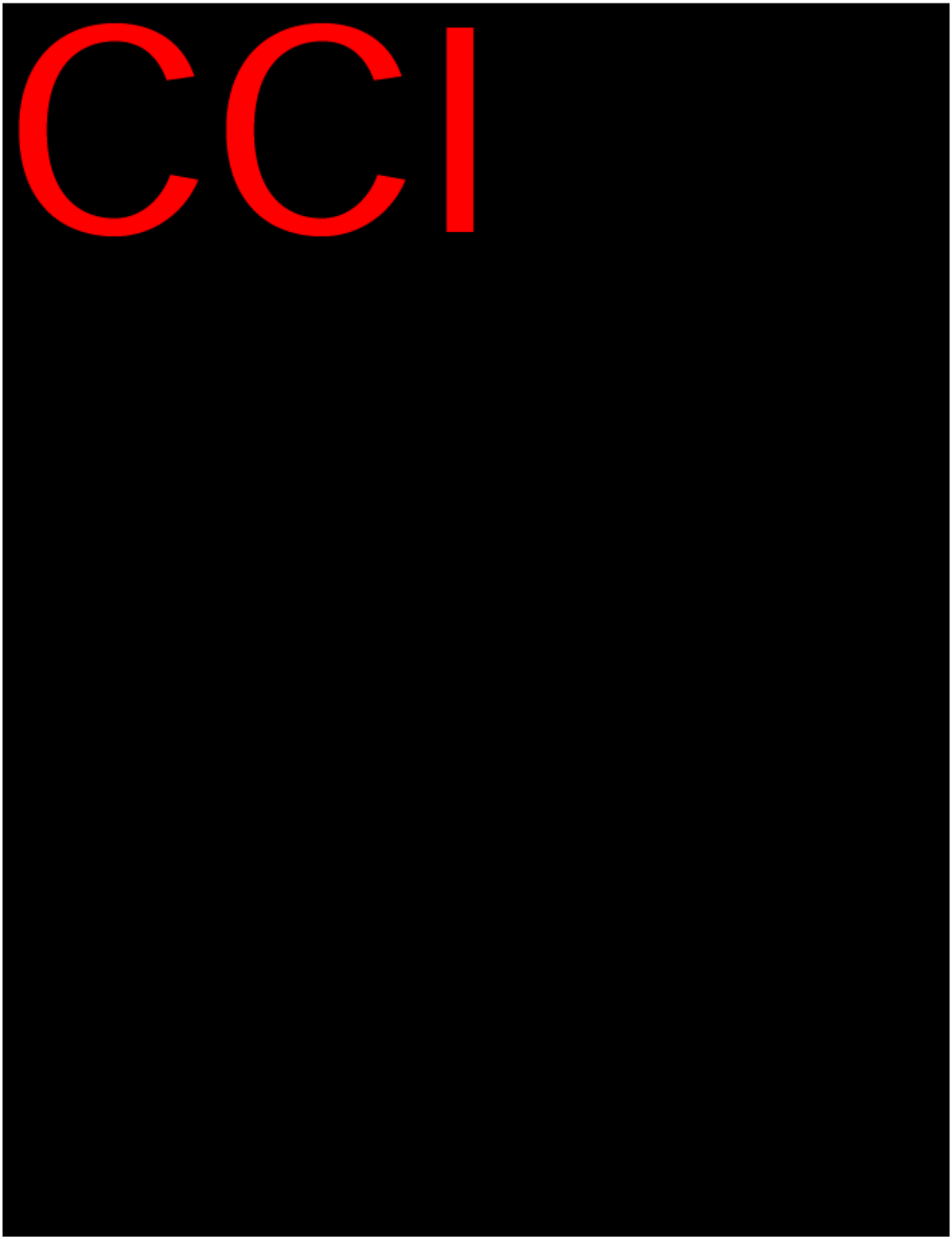
The primary endpoints of the study are the incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).

4.2 Secondary Objective

The secondary objective of the study is to characterize the PK following single or multiple orally administered doses of LY3509754 in healthy participants.

The secondary endpoints of the study are the maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) of LY3509754.

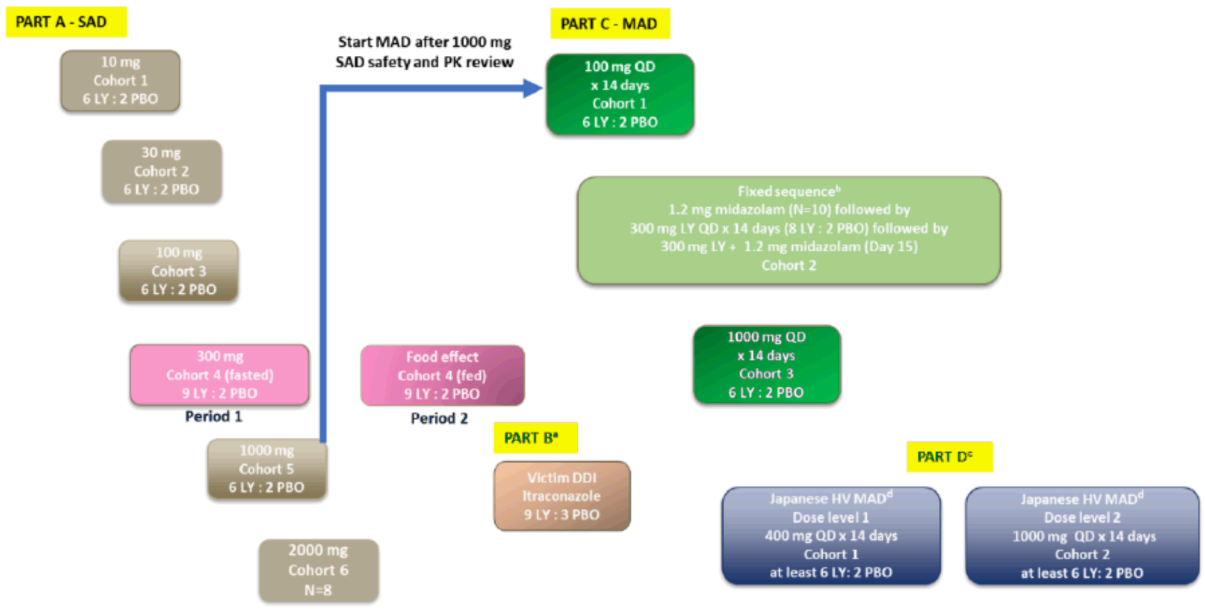
4.3 Exploratory Objectives



5. STUDY DESIGN

Study J3D-MC-FNAA is a Phase 1, multi-center study in healthy participants to be conducted in 4 parts.

A general schema for FNAA can be seen in Figure 1.



Abbreviations: DDI = drug-drug interaction; HV = healthy volunteers; MAD = multiple-ascending dose; QD = once daily; SAD = single-ascending dose; TBD = to be determined.
Schema does not represent start or end times of each study part.

a Part B will begin after emerging safety, tolerability, and PK data from Part A has been reviewed.
b Fixed sequence cohort with 3 dosing events. In the first dosing event, all 10 participants receive midazolam. In the second dosing event, LY3509754 or placebo (8 LY3509754; 2 placebo) will be administered once daily for 14 days. In the third dosing event, both LY3509754 and midazolam will be administered on Day 15.
c Cohorts to run concurrently. At least 12 participants must complete Part D of the study.
d Dose level selected based on the results in the other parts of the study.

Figure 1: A general schema for FNAA

5.1 Part A (Single ascending dose [SAD])

Part A will be a participant-and investigator-blind, placebo-controlled, randomized, SAD study to evaluate safety, tolerability, and PK of LY3509754 in healthy participants in up to 6 cohorts. One cohort (Cohort 4) will include a randomized, single-dose level, 2 period crossover food effect evaluation in participants administered LY3509754 following fasting and a high fat meal (periods 1 and 2, respectively).

Participants will be randomly assigned/enrolled into up to 6 cohorts with up to 51 participants completing this part of the study. Cohorts 1, 2, 3, and 5 will undergo the dose escalation with

6 LY3509754:2 placebo participants completing this part of the study. Cohort 4 will have a total of 11 participants completing a 2-period crossover. In Period 1 of Cohort 4, 11 participants will be randomly assigned (9 LY3509754:2 placebo) to complete the dose escalation part of the SAD study under fasted conditions. The washout between the LY3509754 dosing days in Period 1 and Period 2 for participants in Cohort 4 will be at least 5 days. CCI

ohort 6 will have up to 8 participants completing this part of the study. This cohort may be used for additional safety, tolerability, PK, and food effect evaluation as deemed necessary by the sponsor and in discussion with the investigator following review of emerging safety, tolerability, and PK data from Cohorts 1 through 5.

5.2 Part B (CYP3A4 Inhibition)

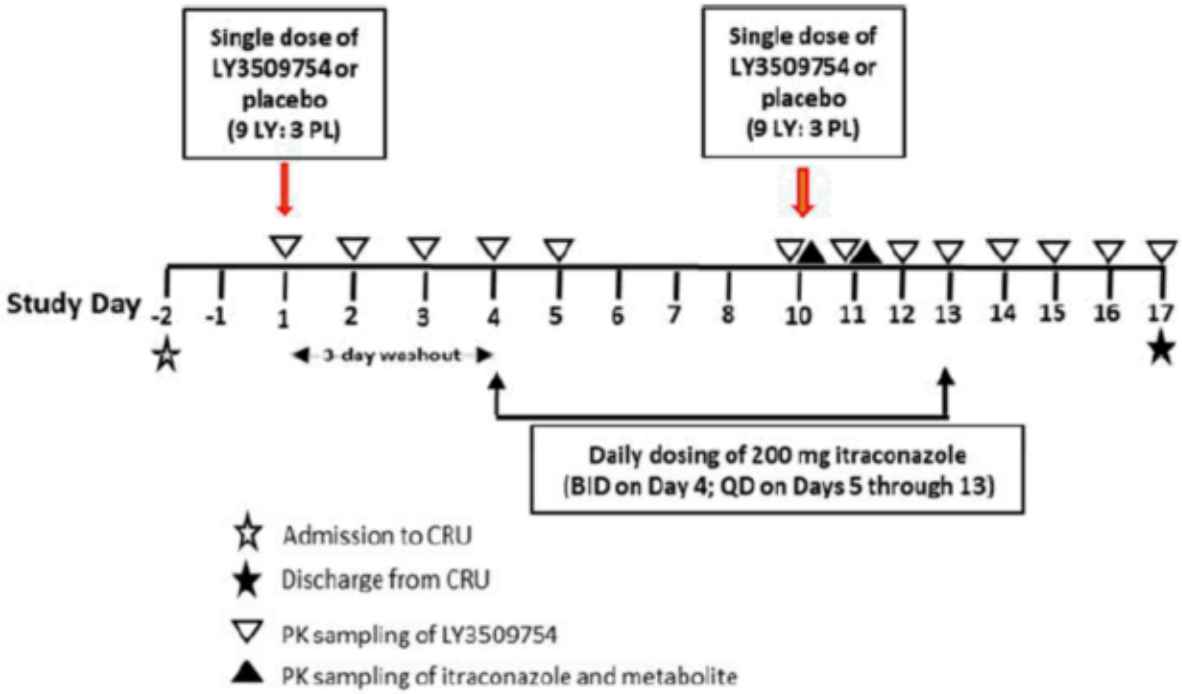
Part B will be a participant- and investigator-blind, placebo-controlled, single-dose-level, single-arm, DDI study to evaluate the multiple dose impact of the CYP3A4 inhibitor, itraconazole, on the single dose exposure of LY3509754.

Participants will be randomly assigned/enrolled with up to 12 participants (9 LY3509754:3 placebo) completing this part of the study. Participants will be admitted to the clinical research unit (CRU) on Day -2 and will undergo an overnight fast before receiving a single oral dose of LY3509754 or placebo on Day 1 and continue fasting approximately 2 hours after dosing. Blood sampling for PK purposes (LY3509754 and itraconazole) will occur. There will be an up to 5-day washout period followed by 10 days of daily dosing with 200 mg itraconazole as an oral solution (twice daily on Day 4 [dose separated by approximately 12 hours], then once daily on Days 5 through 13).

Participants will undergo an overnight fast on Day 9, before receiving a single oral dose of LY3509754 or placebo on Day 10, approximately 1 hour after the dose of itraconazole. Blood sampling for PK purposes (LY3509754 and itraconazole) and other assessments will occur. The timing and duration of the itraconazole dosing may be adjusted based on emerging data from Part A.

Participants will remain in the CRU until discharge on the morning of Day 17, approximately 96 hours after the final dose of itraconazole and approximately 7 days after the final dose of LY3509754. A joint sponsor and investigator safety review will be completed approximately 5 days after each LY3509754 administration. A poststudy follow-up visit will be conducted approximately 7 days after discharge.

The study design for Part B is illustrated in Figure 2.



Abbreviations: BID = twice daily; CRU = clinical research unit; LY = LY3509754; PK = Pharmacokinetic; PL = placebo; QD = once daily.

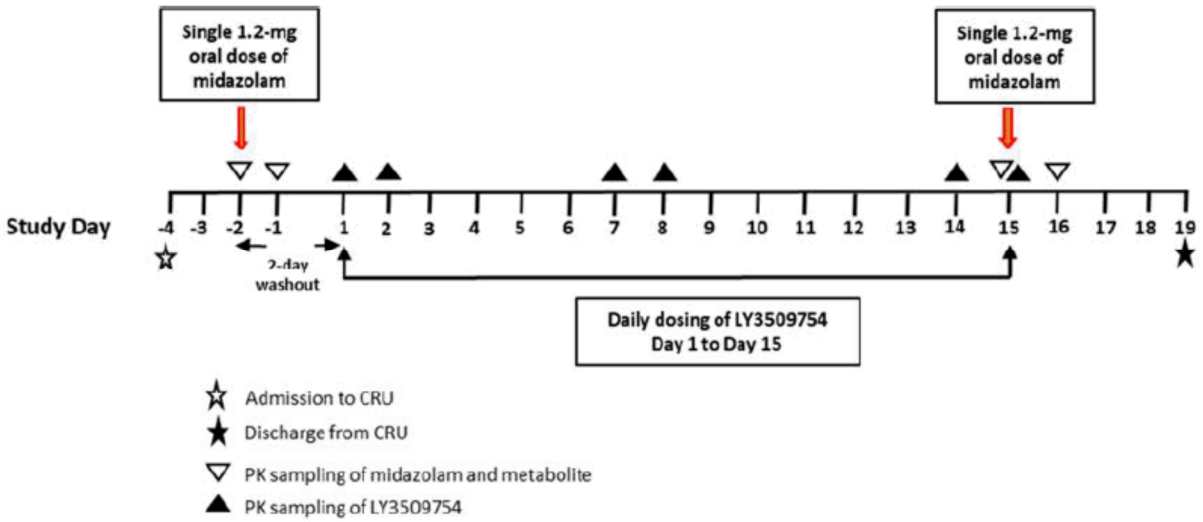
Figure 2: Study design for Part B

5.3 Part C (Multiple ascending dose [MAD]/CYP3A4 Perpetrator DDI)

Part C will be a participant-and investigator-blind, placebo-controlled, randomized, 14-day, single-period MAD study with up to 3 cohorts to evaluate safety, tolerability, and PK of LY3509754 in healthy participants. CCI [redacted]

Participants will be randomly assigned/enrolled into up to 3 cohorts with up to 26 participants completing this part of the study. In 1 cohort, a perpetrator DDI evaluation will be conducted as a fixed, sequence evaluation to understand the impact of LY3509754 (administered as multiple doses to steady state) on midazolam PK. Cohorts 1 and 3 will undergo the dose escalation with 6 LY3509754:2 placebo participants completing this part of the study. Cohort 2 will have a total of 10 participants completing a fixed sequence study. CCI [redacted]

The study design for Part C Cohort 2 is illustrated in Figure 3.



Abbreviations: CRU = clinical research unit; PK = pharmacokinetics.

Figure 3: Study design for Part C Cohort 2

5.4 Part D (Multiple Dosing in Japanese Healthy Participants)

Part D will be a participant-and investigator-blind, placebo-controlled, randomized, multiple dose study to evaluate safety, tolerability, and PK of LY3509754 in healthy Japanese participants in 2 dose levels in 2 separate cohorts (1 dose level per cohort). The 2 dose levels will be run concurrently. Dose level 1 will be the maximum dose to cover the highest exposure dose based on the results in the other parts of the study; and dose level 2 will be selected based on the results in the other parts of the study. It may be necessary for the sponsor, in conjunction with the study site, to re-assess whether it will be practicable to conduct this part of the study because of logistical challenges (e.g., travel restrictions) to gathering healthy Japanese volunteers during the ongoing Coronavirus Disease 2019 (COVID-19) pandemic.

Participants will be randomly assigned/enrolled into up to 2 cohorts with at least 16 participants completing this part of the study. At least 8 participants (6 LY3509754:2 placebo) are completing each dose level.

6. TREATMENTS

The following is a list of the study treatments for Part A that will be used in the TFLs.

Cohort	Period	Study Treatment Name	Treatment order in TFL
All (Period 1 only for Cohort 4)		Placebo (fasted)	1
4	2	Placebo (fed)	2
1		10 mg LY3509754 (fasted)	3

2		30 mg LY3509754 (fasted)	4
3		100 mg LY3509754 (fasted)	5
4	1	300 mg LY3509754 (fasted)	6
	2	300 mg LY3509754 (fed)	7
5		1000 mg LY3509754 (fasted)	8
6*		2000 mg LY3509754 (fasted)	9

* Optional cohort, may also be used for food effect evaluation; if food effect evaluation is used, this will be a two-period fasted/fed cohort.

The following is a list of the study treatments for Part B that will be used in the TFLs.

Study Treatment Name	Treatment order in TFL
Placebo alone (Day 1)	11
Placebo + 200 mg itraconazole (Day 10)	12
200 mg itraconazole (Days 4 to 13)	13
10 mg LY3509754 alone (Day 1)	14
10 mg LY3509754 + 200 mg itraconazole (Day 10)	15

The following is a list of the study treatments for Part C (all cohorts except Cohort 2) that will be used in the TFLs.

Cohort	Study Treatment Name	Treatment order in TFL
All except 2	Placebo QD	16
1	100 mg LY3509754 QD	17
3	1000 mg LY3509754 QD	18

Abbreviations: QD = once daily.

The following is a list of the study treatments for Cohort 2 of Part C that will be used in the TFLs.

Study Treatment Name	Treatment order in TFL
1.2 mg midazolam (Day -2)	20
Placebo QD (Days 1 to 14)	21
300 mg LY3509754 QD (Days 1 to 14)	22
Placebo QD + 1.2 mg midazolam (Day 15)	23
300 mg LY3509754 QD + 1.2 mg midazolam (Day 15)	24

Abbreviations: QD = once daily.

The following is a list of the study treatments for Part D that will be used in the TFLs.

Cohort	Study Treatment Name	Treatment order in TFL
All	Placebo QD	25
1	400 mg LY3509754 QD	26
2	1000 mg LY3509754 QD	27

Abbreviations: QD = once daily.

7. SAMPLE SIZE JUSTIFICATION

The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK, and is not powered on the basis of any a priori statistical hypothesis testing. The sample sizes for all parts of the study are based upon previous studies.

Participants who are randomized but not administered treatment may be replaced to ensure that adequate participant data will be available for safety and exposure assessments in this phase of clinical development. The replacement participant should be assigned to the same treatment arm as the discontinued participant.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled participants, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all participants who received at least one dose of LY3509754, itraconazole, or midazolam, have evaluable PK data, and have pre-dose 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 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, split by study part. 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 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, 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

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) will be used.

Part A (SAD) and Part B (DDI - CYP3A4 victim)

Urine (Part A only) and plasma concentrations of LY3509754 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
AUC(0-24)	ng.h/mL	area under the concentration versus time curve from time zero to 24 hours postdose
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	H	time of maximum observed drug concentration
t_{last}	H	time of last observed drug concentration
$t_{1/2}$	H	half-life associated with the terminal rate constant (λz) 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
Ae	Mg	amount of drug excreted
Fe	%	fraction of dose excreted unchanged
CL_R	L/h	renal clearance

In Part B, if available, plasma concentration data for itraconazole and its hydroxyitraconazole metabolite will be listed in the study report. A PK analysis of itraconazole and its hydroxyitraconazole metabolite may be conducted if deemed valuable to the interpretation of the study results but is not required to complete the CSR.

Part C (MAD) and Part D (Japanese Participants)
Plasma concentrations of midazolam and its 1-hydroxymidazolam metabolite (in Part C), and LY3509754 will be used to determine the following PK parameters, when possible:

Midazolam and its 1-hydroxymidazolam metabolite

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
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
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration

LY3509754

Parameter	Units	Definition
AUCτ	ng.h/mL	area under the concentration versus time curve during the dosing interval (τ = 24 hours)
AUC(0-24)	ng.h/mL	area under the concentration versus time curve from time zero to 24 hours postdose
C_{max}	ng/mL	maximum observed drug concentration
$C_{predose}$	ng/mL	predose 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
R_A(AUC)	NA	accumulation ratio based upon AUC(0-24)/AUCτ

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 study report.

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.

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

- The 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 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.

- 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. The $t_{1/2}$ 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 will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters 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 quantification (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 minimum quantifiable drug concentration for the dosing interval.

For urine PK analysis, all BQL concentrations will be set to zero.

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 study report.
- 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 Pharmacokinetic 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 multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- 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 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.

The accumulation ratio will be calculated, based on AUCτ, using the equation

$$\text{RA(AUC)} = \frac{AUC(multiple\ Dose\ PK\ Day)}{AUC(Day\ 1)}$$

Multiple Dose PK Day = Day 7 and Day 14

9.3.2 Pharmacokinetic Statistical Methodology

Part A (SAD)

Dose proportionality

On Day 1 of each cohort (Period 1 only for Cohort 4 and any of the optional cohort assessing food effect), log-transformed C_{max}, AUC(0-∞), AUC(0-t_{last}), and AUC(0-24) parameters of LY3509754 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals (CIs). The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach. Between patient estimates will also be provided.

Example of the SAS code for the analysis:

```
proc mixed data=xxx;
model log_pk = log_dose / alpha=0.1 cl solution outpred=resids ddfm=kr;
estimate 'xx mg' intercept 1 log_dose yy / alpha=0.1 cl; /*Log value of xx*/
estimate 'zz mg - xx mg' log_dose pp / alpha=0.1 cl; /*Difference in log
values of zz and xx*/
ods output solutionf=est;
ods output estimates=estims;
run;
```

Food effect (Cohort 4)

Log-transformed C_{max}, AUC(0-∞), AUC(0-t_{last}), and AUC(0-24) parameters of LY3509754 will be compared in the fed and fasted state to explore the effect that food has on the PK parameters. A mixed-effect analysis of variance (ANOVA) model will be fit to the data. The model will include a fixed effect for the treatment (fed or fasted) and a random effect for participant. The ratio of least squares (LS) geometric means for the LY3509754 in a fed state compared to fasted state, as well as the 90% CI of the ratio will be estimated and reported.

Example of the SAS code for the analysis:

```
proc mixed data=xxx alpha=0.1;
class treat subjid;
```

```
model log_pk = treat /residual ddfm=kr;
random subjid;
lsmeans treat / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

The t_{max} of LY3509754 will be analyzed non-parametrically using a Wilcoxon signed-rank test. An estimate of the median difference, comparing fed (test) to fasted (reference), and corresponding 90% CI for the difference between treatments will be calculated and presented, alongside the p-value from the Wilcoxon signed-rank test.

Example SAS code to be used for the Wilcoxon signed-rank test:

```
proc univariate data = xxx cipctldf(alpha = 0.1);
var ref test dif;
ods output quantiles = quant;
ods output testsforlocation = out;
run;
```

If any of the optional cohorts are also used to assess the food effect, then its data will be analyzed similarly to Cohort 4.

Part B (DDI - CYP3A4 victim)

Log-transformed C_{max}, AUC(0-∞), AUC(0-t_{last}), and AUC(0-24) parameters will be analyzed using an ANOVA model to compare LY3509754 administered alone, and LY3509754 administered with itraconazole. The model will include a fixed effect for treatment, and a random effect for participant. The LS means for each treatment, the difference between the treatment LS means (LY3509754 + itraconazole – LY3509754 alone), and the associated 90% CIs will be estimated from the ANOVA model and back-transformed from the log scale to provide estimates of the geometric means, geometric mean ratio, and corresponding 90% CIs.

Example of the SAS code to be used for the ANOVA model:

```
proc mixed data=xxx alpha=0.1;
class treat subjid;
model log_pk = treat /residual ddfm=kr;
random subjid;
lsmeans treat / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

Part C (MAD)

Dose proportionality (all cohorts except 2)

The methodology of this will be the same as Part A, with the parameters C_{max} and AUCτ used to assess dose proportionality. The analysis will be done for both Days 1 and 14.

Midazolam analysis (Cohort 2)

Log-transformed AUC(0-∞) and C_{max} midazolam parameters will be analyzed using a linear mixed effects model to assess the effect that LY3509754 has on the PK parameters of midazolam. The model will include treatment as a fixed effect, and participants included as a random effect. The LS means for each treatment, the difference between the treatment LS means (midazolam [Day -2] alone - LY3509754 + midazolam [Day 15]), and the associated 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means, geometric mean ratio, and corresponding 90% CIs.

Example of the SAS code to be used for the mixed-effect model:

```
proc mixed data=xxx alpha=0.1;
class treat subjid;
model log_pk = treat /residual ddfm=kr;
random subjid;
lsmeans treat / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

Part D (Japanese Participants)

The LY3509754 PK parameters will be compared between Japanese and non-Japanese participants. Descriptive statistics for C_{max}, AUCτ, t_{max}, terminal half-life, apparent clearance, and apparent volume of distribution will be included in the tabular comparisons. Body-weight normalized and dose-normalized PK parameters may be calculated for both Part C and Part D for comparison. Graphical comparisons of C_{max}, AUCτ, and concentration-time profiles will also be prepared.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form, each separate severity of the adverse event (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 an AE 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 the first dose. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to the first dose 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 23.0 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. For Parts C and D, AEs by day of onset will be presented.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version WHO Drug Global March 2020 B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by part, parameter and treatment, 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 together with changes from baseline, where baseline is defined as the following assessments:

- Part A (except Cohort 4) – Day 1 predose
- Part A Cohort 4 – Day 1 predose of respective period
- Part B – Day 1 predose and Day 10 predose for respective profiles
- Part C – Day 1 predose
- Part D – Day 1 predose.

Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

9.4.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QRS duration and HR. In addition, QT interval corrected using Fridericia's formula (QTcF) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

Where ECG data are measured in triplicate, the mean value will be calculated and used in all subsequent calculations.

The ECG data will be summarized by part and treatment, together with changes from baseline, where baseline is defined as the Day 1 predose assessment for single ECG data, and the mean of the triplicate Day 1 predose assessment for the triplicate ECG data in Part A and Part D. Figures of mean ECG data and mean changes from baseline will be presented by part and treatment. The frequency of participants with a maximum increase from baseline in QTcF interval will be

summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of participants with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

Plasma PK Concentration versus Delta and Double Delta ECG Parameter Analysis (Part A)

A plasma LY3509754 concentration-ECG parameter analysis will be performed to assess the relationship between changes from baseline (mean of Day 1 predose triplicate assessment) in ECG parameters (QTcF, PR interval, QRS duration, and HR) and plasma LY3509754 concentrations across all fasted treatments. The change from baseline adjustment will be based on individual participant's Day 1 predose value. Only matching PK and ECG parameter timepoints will be included in the analysis. Further details on how these will be calculated:

- Calculate the change from baseline at each postdose timepoint for each individual participant.
- Calculate the mean ECG parameter value across all participants at baseline.
- For each participant subtract the mean ECG parameter value from their own individual observed ECG parameter value. This will be each participant's centered baseline ECG parameter value.
- Postdose BQL LY3509754 concentration data will be treated as missing (no imputation).

The relationship between LY3509754 concentrations and ECG parameters will be explored graphically by plotting delta ECG, which is defined as the change from baseline of the ECG parameter values against LY3509754 concentrations, including all post dosing timepoints. Double delta ECG, which is defined as the placebo-corrected change from baseline of the ECG will also be plotted.

A mixed effects analysis model will be employed with change from baseline in ECG parameter as the dependent variable, LY3509754 concentration and centered ECG parameter value as continuous covariates, treatment (LY3509754 or placebo) and time as categorical factors, and a random intercept and slope of concentration per participant. Treatment will be fitted as a binary variable (Placebo, or LY3509754). The model will have the form[3]

$$\Delta ECG_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_{3k} TIME_k + \theta_4 (ECG_{i,j,k=0} - \overline{ECG_{k=0}}) + \varepsilon_{ijk}$$

where ΔECG_{ijk} is the change from baseline in ECG parameter for participant i in treatment j at time k, with k starting from the first post-dose timepoint; θ_0 is the population mean intercept in the absence of treatment effect, $\eta_{0,i}$ is the random effect associated with the intercept term θ_0, θ_1 is the fixed effect categorical variable associated with treatment TRT_j (i.e. LY3509754), θ_2 is the population mean slope of the assumed linear association between concentration and ΔECG_{ijk}, $\eta_{2,i}$ is the random effect associated with the slope θ_2, C_{ijk} is the concentration for participant i in treatment j and time k, θ_{3k} is the fixed effect associated with time k, θ_4 is the fixed effect associated with baseline $ECG_{i,j,k=0}$, $\overline{ECG_{k=0}}$ is the overall mean of $ECG_{i,j,k=0}$ (the mean of all the baseline ECG parameter values, at predose), and ε_{ijk} is the residual error. It will be assumed the

random effects are multivariate Gaussian distributed with mean vector 0 and an unstructured covariance matrix G, whereas the residuals, ε_{ijk}, are Gaussian distributed with mean 0 and variance r.

The predicted placebo-corrected change from baseline in ECG parameter (ΔΔECG) at the observed geometric mean C_{max} of each dose and two-sided 90% CI at different dose levels will be calculated. Hysteresis loop plots of delta ECG parameters versus LY3509754 plasma concentrations for the first 24 h, and scatter plots of paired ΔECG versus PK concentration with a linear regression line with a 90% CIwill also be provided. Residual plots will be produced to assess the adequacy of the model.
Example of SAS code as follows:

```
proc mixed data=xxx;
by param;
class treat time patient;
model ΔECG = treat time centred_baseline_ECG PKconc / solution cl alpha=0.1
ddfm=kr;
random intercept PKconc / type=un subject=patient;
estimate 'Placebo ' intercept 1 treat 1 0 PKconc 0/ CL alpha=0.1;
estimate 'YY mg LY3509754 ' intercept 1 treat 0 1 PKconc [geomean of cmax
YYmg] / CL alpha=0.1;
estimate 'YY mg LY3509754 - Placebo' treat -1 1 PKconc [geomean of cmax cmax
YYmg] / CL alpha=0.1;
ods output covparms=covp(where=(covparm="Residual"));
ods output solutionF=sol;
ods output estimates=estim;
run;
```

Plasma PK Concentration versus Delta and Double Delta ECG Parameter Analysis (Part D)

A plasma LY3509754 concentration-ECG parameter analysis will be performed for the first 24 hours of data for Part D, in the same approach as that described for Part A above.

As the variability of this study is higher than expected and this study is unable to rule out 10 msec at a clinically relevant concentration, it may be combined with the data from the Part A for an omnibus concentration/response.

9.4.6 Hepatic Monitoring

If a participant experiences elevated alanine aminotransferase ≥3× upper limit of normal (ULN), alkaline phosphatase ≥2× ULN, or elevated total bilirubin ≥2× ULN, liver 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. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen 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 COVID-19 Assessments

The data collected from the COVID-19 tests will be listed by part, if available.

9.5 Biomarker Data

All biomarker data, including, but not limited to IL-17 and IL-19, will be listed by part and treatment, if available.

9.5.1 Other assessments

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

10. INTERIM ANALYSES

No formal interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

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. Garnett, Christine & Bonate, Peter & Dang, Qianyu & Ferber, Georg & Huang, Dalong & Liu, Jiang & Mehrotra, Devan & Riley, Steve & Sager, Philip & Tornoe, Christoffer & Wang, Yaning. (2017). Scientific white paper on concentration-QTc modeling. Journal of Pharmacokinetics and Pharmacodynamics. 45. 1-15. 10.1007/s10928-017-9558-5.

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	13 Sep 2021	Updated to reflect updated made in protocol amendments (a), (b), (c), and (d) and to add details for QTc analysis for Part D and Part A and D combined.

NA = not applicable

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