Statistical Analysis Plan J1Z-MC-HUAA

Single- and Multiple-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study with LY3154885 in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

Single- and Multiple-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study with LY3154885 in Healthy Subjects

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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]).

ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AUC	Area under the concentration versus time curve
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DSST	Digital Symbol Substitution Test
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: exempli gratia)
HVLT	Hopkins Verbal Learning Test
ICH	International Conference on Harmonisation
LS	Least square
MAD	Multiple ascending dose
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PD	Pharmacodynamic
PK	Pharmacokinetic

POMS-2	Profile of Mood States Second Edition
PR	Pulse rate
PWC-20	Penn Physician Withdrawal Checklist
SAD	Single ascending dose
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 07 May 2019) and amendment (a) (dated 21 June 2019).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) 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 between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. 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 signed off prior to first subject administration of study drug 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 between Eli Lilly and Company and Covance EC Biometrics 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

- To explore the safety and tolerability of single and multiple doses of LY3154885 in healthy subjects

4.2 Secondary Objectives

- To determine the PK of LY3154885 following administration of single and multiple oral doses of LY3154885
- To determine the PK of LY3154885 when administered with itraconazole (Part B only)
- To assess safety and tolerability of LY3154885 when administered with itraconazole (Part B only)
- To compare the PK of LY3154885 when administered with a capsule or tablet formulation (Part D only)
- To evaluate the effect of a high-fat diet on the PK of LY3154885 (Part D only)

4.3 Exploratory Objectives (Part C Only)

- To explore any procognitive effects of LY3154885 in healthy subjects using the Hopkins Verbal Learning Test (HVLT) and Digital Symbol Substitution Test (DSST)
- To explore the effect of LY3154885 on subjective mood using the Profile of Mood States Second Edition (POMS-2)
- To evaluate any potential withdrawal symptoms following multiple once-daily dosing of LY3154885

5. STUDY DESIGN

This is a Phase 1, single-center study in healthy subjects to be conducted in 4 parts:

- Part A will be a subject- and investigator-blind, placebo-controlled, randomized, single ascending dose (SAD), 3-period crossover study to evaluate safety, tolerability, and PK of LY3154885 in 2 alternating cohorts.
- Part B will be a subject- and investigator-blind to LY3154885/placebo, single-period, drug-drug interaction study with itraconazole.
- Part C will be a subject- and investigator-blind, placebo-controlled, randomized, 14-day multiple-ascending dose (MAD), parallel-group, 3-cohort, single-period study to evaluate safety, tolerability, and PK of LY3154885.
- Optional Part D will be an open-label, 3-period 3-sequence PK study of LY3154885 administered using a capsule or tablet formulation. Part D will also include a pilot food effect evaluation.

5.1 Part A (Single-Ascending Dose)

Part A will be conducted in 2 alternating cohorts (Cohorts 1 and 2), each consisting of approximately 12 subjects who will participate in up to 3 study periods. The planned doses of LY3154885 to be tested are 15, 45, 100, 200, 400, and 500 mg.

Sentinel dosing will be used in Part A of the study. For all dose levels, LY3154885 and placebo will be administered first to 2 subjects (1:1 LY3154885:Placebo) in a blinded manner. These subjects will be followed up for 24 hours postdose; if the dose is well tolerated, dosing of the remaining 10 subjects in the cohort at the same dose level may begin.

Each subject in Cohorts 1 and 2 will be randomized to receive 2 single oral doses of LY3154885 and 1 oral dose of placebo as a capsule formulation over 3 study periods in a crossover fashion. For each study period, it is intended that 8 subjects will receive LY3154885 and 4 subjects will receive placebo.

In Period 1, subjects will be admitted to the clinical research unit (CRU) on the evening of Day -2. A 24 hour baseline ambulatory blood pressure monitoring (ABPM) recording on Day -1 of Period 1. ABPM recording on dosing days will be initiated 2 hours prior to dose for Periods 1, 2 and 3. Subjects will undergo an overnight fast before dosing with LY3154885 or placebo as a single oral dose on Day 1 and will remain inpatient for at least 48 hours after dosing (until Day 3), after which they may be discharged at the discretion of the investigator. The washout time

between doses for a given subject will be at least 7 days. A post study follow-up visit will be conducted at least 7 days after the final dose.

All available safety data, including adverse events (AEs), vital signs (blood pressure [BP] and pulse rate [PR]), electrocardiogram (ECGs), and clinical laboratory tests, from all subjects dosed will be assessed prior to escalating to the next dose level. Safety data must include data from at least 2 days from a minimum of 6 subjects who received LY3154885. The investigator and sponsor will review the data, with the investigator remaining blinded. If dose escalation is terminated prior to reaching Dose 6 because of tolerability issues, previous dose levels may be repeated or lower/intermediate dose levels may be tested.

Subjects will provide total urine collections for the 36 hours postdose in each period for exploratory metabolism and potential assessment of drug absorption and renal elimination; an additional blood sample will be collected to determine serum creatinine measurements. The figure below illustrates the study design for Part A.

	Period 1		Period 2		Period 3	
Cohort 1 (n=12; 8LY:4PL)	Dose 1 LY or PL	≥7 day washout	Dose 3 LY or PL	≥7 day washout	Dose 5 LY or PL	≥7 day washout
Cohort 2 (n=12; 8LY:4PL)		Dose 2 LY or PL	≥7 day washout	Dose 4 LY or PL	≥7 day washout	Dose 6 LY or PL

Safety review completed after each dose level prior to escalation

Abbreviations: LY = LY3154885; n = number of subjects; PL = placebo.
Each subject will receive 2 doses of LY3154885 and 1 placebo dose.

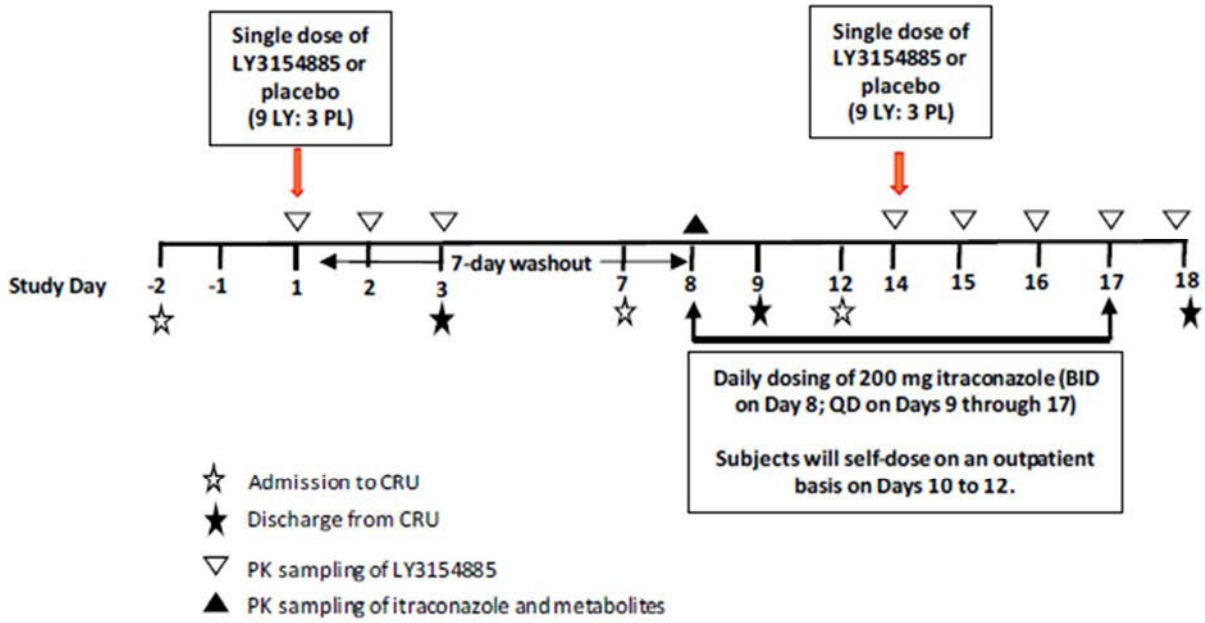
5.2 Part B [Cytochrome P450 (CYP) 3A4 inhibition Inhibition]

Part B will consist of approximately 12 subjects [9 LY3154885; 3 placebo] and will assess the effect of itraconazole, a CYP3A4 inhibitor, on the safety, tolerability, and PK of LY3154885. The LY3154885 dose to be studied in Part B will be determined based on safety, tolerability, and PK data from Part A and will be administered as a capsule formulation.

Subjects will be admitted to the CRU on the evening of Day -2. A 24 hours baseline ABPM will be recorded on Day -1. A 2 hrs ABPM measure will be initiated prior to dose time. Subjects will undergo an overnight fast before receiving a single oral dose of LY3154885 or placebo on Day 1. Subjects may be discharged from the CRU on Day 3 and will be re-admitted on Day 7. There will be a 7-day washout period followed by 10 days of dosing with 200 mg itraconazole (twice daily on Day 8 [dose separated by 12 hours], then once daily on Days 9 through 17). Subjects

will be discharged from the CRU on Day 9 after receiving their dose of itraconazole and will be self-dosing on an outpatient basis from Days 10 through 12. Subjects will be asked to complete a diary card to document the actual date and time of dose administration.

Subjects will be re-admitted to the CRU in the evening of Day 12 and will undergo an overnight fast before receiving a single oral dose of LY3154885 or placebo on Day 14, approximately 1 hour after the dose of itraconazole. Blood sampling for PK purposes (LY3154885 and itraconazole) will occur according to the scheduled timepoints. Subjects will remain in the CRU until discharge on the morning of Day 18, approximately 24 hours after the final dose of itraconazole. The figure below illustrates the study design for Part B.



Abbreviations: BID = twice daily; CRU = clinical research unit; LY = LY3154885; PK = pharmacokinetic; PL = placebo; QD = once daily.

5.3 Part C (Multiple-Ascending Dose)

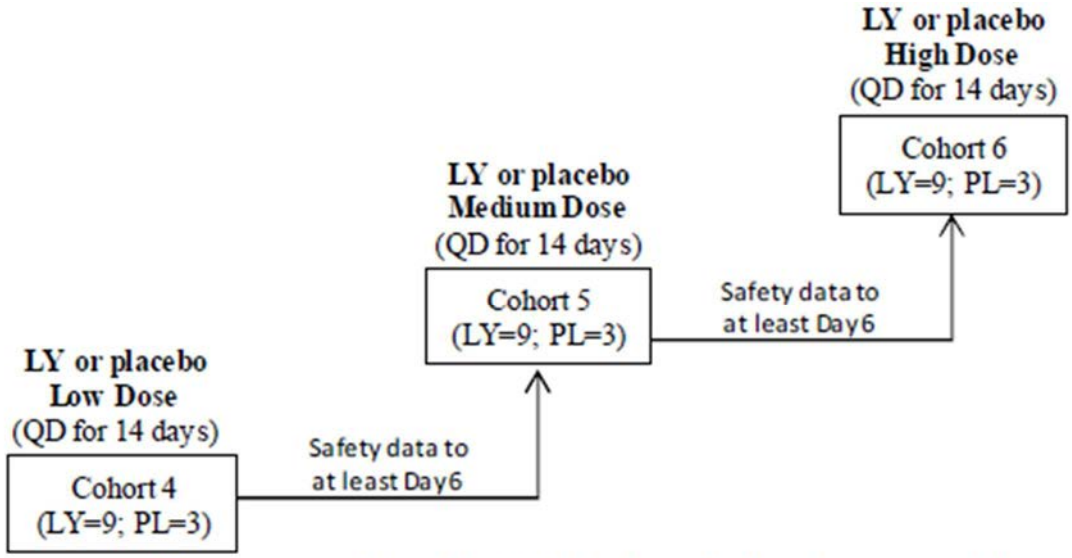
The decision to conduct Part C will be made after review of safety, tolerability, and PK data from Parts A (SAD) and B (CYP3A4 Inhibition).

Part C will explore up to 3 dose levels in 3 separate cohorts (Cohorts 4 to 6) of healthy subjects. Each cohort will consist of approximately 12 subjects (9 LY3154885; 3 placebo) dosed daily for 14 days with a capsule formulation.

Subjects will participate in a single study period consisting of 14 days of once-daily dosing with LY3154885 or placebo; study drug will be administered as a single oral dose in the morning under fasted conditions. Subjects will be admitted to the CRU on the evening of Day -2. A 24 hour baseline ABPM will be recorded on Day -1. and a 2 hours ABPM will be initiated on Day 1 prior to dose. Subject will be required to remain inhouse for at least 48 hours after dosing (Day 3), and at the discretion of the investigator. Subjects will attend the CRU on Days 4, 5, 6, 9, and 10 on an outpatient basis for daily dosing and will be permitted to leave the CRU at the

discretion of the investigator. PK sampling will be conducted. To assess cardiovascular effects and potential accommodation over time, ABPM will be included on Day -1 (baseline) and on Days 1, 2, 7, 11, 12, and 14. A poststudy follow-up visit will be conducted approximately 7 days after discharge.

The doses evaluated will be selected based on emerging data from Parts A and B and from the lower doses from Part C. If the safety data do not support increasing the dose in subsequent cohorts, then a dose may be repeated or lower/intermediate doses may be explored. The PK data obtained during the study may be used to assist in dose-escalation decisions, but such data are not required for dose-escalation purposes. For the safety review prior to dose decisions between cohorts, all available safety data (AEs, vital signs, ECGs, and laboratory results) to at least Day 6 from at least 6 subjects taking LY3154885 must be reviewed by the sponsor and investigator. In addition, each cohort (including at least 6 subjects treated with LY3154885) will complete dosing to Day 14 prior to the next cohort being admitted to the CRU for dosing. The figure below illustrates the study design for Part C.



Abbreviations: LY = LY3154885; PL = placebo; QD = once daily.

5.4 Optional Part D (Pharmacokinetics of Capsule and Tablet Formulations and Food Effect)

The decision to conduct Part D will be made after review of safety, tolerability, and PK data from Parts A (SAD) and B (CYP3A4 Inhibition). Part D may be conducted in parallel with Part C.

Part D is optional and will assess the PK of single oral doses of LY3154885 in approximately 9 healthy subjects when administered as a capsule (Period 1), as a tablet (Period 2), and as a tablet with a high-fat diet (Period 3). The dose for Part D will not exceed the highest dose tested in Part A (SAD) that was deemed safe and well tolerated.

In Periods 1 and 2, subjects will be admitted to the CRU the evening of Day -2. A 24 hours baseline ABPM will be recorded on Day -1. A 2 hours ABPM will be initiated prior to dose in

each Period. Subject's admission for Period 3 will be on Day -1. In Period 1, subjects will undergo an overnight fast before receiving a single oral dose of LY3154885 (capsule formulation) on Day 1. Subjects will remain inpatient for at least 48 hours after dosing, after which they may be discharged at the discretion of the investigator. Subjects will be re-admitted to the CRU on Day 6 and will undergo an overnight fast before receiving a subsequent single oral dose of LY3154885 on Day 8 with the same formulation. Subjects will be discharged on Day 10, at least 48 hours after dosing. Re-admission to the CRU will be on Day 13, and following an overnight fast, subjects will receive a single oral dose of LY3154885 on Day 14 with the same formulation.

Final discharge from the CRU will occur on Day 16.

Period 2 will be conducted as described for Period 1; however, LY3154885 will be administered as a tablet formulation. Period 3 will be conducted as described for Period 1; however, subjects will receive a single oral dose of LY3154885 (tablet formulation) after administration of a high-fat diet.

The follow-up visit will occur approximately 7 days after final discharge. The figure below illustrates the study design for Part C.

	Period 1		Period 2		Period 3	
LY3154885 n=9	LY3154885 capsule (Days 1, 8 and 14)	≥7 day washout	LY3154885 tablet (Days 1, 8 and 14)	≥7 day washout	LY3154885 tablet after high fat meal (Days 1, 8 and 14)	≥7 day washout

Intensive PK sampling on Days 1, 8, and 14

Abbreviation: n = number of subjects; PK = pharmacokinetic.

6. TREATMENTS

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

Part	Study Treatment Name	Treatment order in TFL
Part A	Placebo	1
	15 mg LY3154885	2
	45 mg LY3154885	3
	100 mg LY3154885	4
	200 mg LY3154885	5
	400 mg LY3154885	6
	500 mg LY3154885	7
Part B	Placebo	1

	B mg LY3154885	2
	200 mg itraconazole	3
	Placebo + 200 mg itraconazole	4
	B mg LY3154885 + 200 mg itraconazole	5
Part C	Placebo	1
	C1 mg LY3154885	2
	C2 mg LY3154885	3
	C3 mg LY3154885	4
Part D	D mg LY3154885 capsule	1
	D mg LY3154885 tablet	2
	D mg LY3154885 tablet (fed)	3

7. SAMPLE SIZE JUSTIFICATION

For Part A, up to 30 subjects may be enrolled into Cohorts 1 and 2 in order to ensure that approximately 12 subjects per cohort (8 LY3154885; 4 placebo) complete this part of the study.

For Part B, up to 15 subjects may be enrolled in order to ensure that approximately 12 subjects (9 LY3154885, 3 placebo) complete this part of the study.

For Part C, up to 45 subjects may be enrolled in order to ensure that approximately 36 subjects complete this part of the study (with approximately 12 subjects [9 LY3154885; 3 placebo] completing each dose level).

For Part D, up to 12 subjects may be enrolled in order to ensure that approximately 9 subjects complete this part of the study.

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized but not administered treatment or do not complete all treatment periods/doses may be replaced to ensure that enough subjects complete all parts of the study. Replacement subjects will be allocated the same treatment/sequence as the dropout subjects. In Part A, a replacement subject's treatment assignment will follow that of the subject being replaced but may not require completion of all study periods.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of LY3154885 or placebo.

The "PK" population will consist of all subjects who received at least one dose of LY3154885 and have evaluable PK data.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects 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) 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 subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects 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 subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject'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 Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized by part and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates for LY3154885 will be calculated by standard noncompartmental analysis methods. Parameters for analysis will be maximum observed drug concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration versus time curve (AUC) of LY3154885 following single and multiple doses of LY3154885. Following multiple dosing, accumulation ratios based on LY3154885 AUC will be calculated as follows: AUC Day 14 / AUC Day 1 and AUC Day 7 / AUC Day 1. Other PK parameters such as half-life, apparent clearance, and apparent volume of distribution may be reported using noncompartmental analysis methods.

If appropriate data are obtained, renal clearance of LY3154885 will be calculated as the ratio of amount excreted/AUC. This will be compared to the unbound glomerular filtration rate, which is estimated using creatinine clearance.

If available, plasma concentration data for itraconazole and its metabolites (if applicable) will be summarized or listed in the CSR, and the data may subsequently be used for exploratory model development. A noncompartmental PK analysis of itraconazole and its metabolites may be conducted if deemed valuable to the interpretation of the study results but is not required to complete the CSR.

9.3.2 Pharmacokinetic Statistical Methodology

Statistical analysis of the PK parameters will be produced by Covance. All summary outputs will be produced by Lilly.

Part A: The PK parameters C_{max} and AUC for LY3154885 will be evaluated to estimate the dose-exposure proportionality of LY3154885 using a linear-mixed-effect power model. In this model, log-transformed dose will be the independent variable and subject will be a random effect. Both C_{max} and AUC will be log-transformed prior to analysis. The least-squares (LS) means for each treatment together with the treatment differences and associated 90% confidence intervals (CIs) will be estimated from the model. These estimates will be back-transformed to present geometric means, the ratios of geometric means, and the corresponding 90% CIs.

Example SAS code for the analysis:

```
proc mixed data=xxx;
class subject;
model log_pk = log_dose / alpha=0.1 cl solution outpred=resids ddfm=kr;
random subject;
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 estimates=estims;
run;
```

Part B: The PK parameters C_{max} and AUC for LY3154885 when administered alone and with itraconazole will be compared using an analysis of variance (ANOVA) model. The parameters will be log-transformed prior to analysis. The model will include a fixed-effect for the treatment (LY + itraconazole : LY) and a random effect for subject. The LS means for each treatment, the difference between the treatment LS means (LY3154885 + itraconazole – LY3154885), 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 SAS code for the analysis:

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

The t_{max} of LY3154885 for both treatments will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and 90% CI will be calculated.

Part C: The plasma PK parameters C_{max} and AUC for LY3154885 obtained on Day 14 will be evaluated to estimate the dose-exposure proportionality of LY3154885 using a linear-mixed-effect power model. The model used will be the same as Part A above but without subject as a random effect.

Part D:

Effect of formulation: The AUC and C_{max} for LY3154885 following administration of a capsule and tablet formulation in a fasted state will be log transformed and analyzed using a mixed effects ANOVA model. The model will include fixed effects for formulation (capsule : tablet) and a random effect for subject. The LS means for each formulation and the 90% CI for the difference in means will be estimated from the ANOVA model and back-transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the means.

The t_{max} of LY3154885 between formulations will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and 90% CI will be calculated.

Effect of high-fat diet: The AUC and C_{max} for LY3154885 following administration of a tablet formulation in the fed state and fasted state will be log transformed and analyzed using a mixed-effects ANOVA model. The model will include fixed effects for food (fed : fasted) and a random effect for subject. The LS means for fed and fasted and the 90% CI for the difference in means will be estimated from the ANOVA model and back-transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the means.

The t_{max} of LY3154885 between fed and fasted will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and 90% CI will be calculated.

The SAS code for both analyses will be similar to the Part B analysis.

9.4 Pharmacodynamic Assessment

9.4.1 Exploratory Pharmacodynamic Analysis

The DSST and HVLT will be included in Part C to assess relevant aspects of cognition, vigilance, and working memory that may provide a PD signal in healthy volunteers.

Endpoints from the DSST and HVLT will be summarized by domain (as appropriate), time, and treatment. Change from baseline (predose) will also be presented.

POMS-2: a profile of mood states is also included in Part C to assess subject transient, fluctuation feelings and enduring affect states. POMS-2 is a 35-item, adjective rating scale and is considered to be a standardized mood-state inventory. The change from baseline (predose) may be presented as applicable.

9.5 Safety and Tolerability Assessments

9.5.1 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 an AE that starts before the subject 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 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. Treatment-emergent AEs will be summarized by part, treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by part, treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 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. Any serious AEs will be listed. For Part B only, AEs by day of onset will be presented.

9.5.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization drug dictionary (Version September 2018). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by part, parameter and treatment, and listed. Where postdose data is available, changes from baseline, where baseline is defined as Day 1 predose will also be presented. Urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual subject data listings.

9.5.4 Vital signs

Vital signs data will be summarized by part, treatment and timepoint, 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 part and treatment.

Values for individual subjects will be listed.

9.5.5 Electrocardiogram

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

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

The ECG data will be summarized by part, treatment and timepoint, together with changes from baseline, where baseline is defined as the mean of the triplicate assessment. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of subjects 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 subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

9.5.5.1 Electrocardiogram analysis (Part A)

The relationship between the time-matched LY3154885 concentrations and changes from baseline and time-matched placebo in QTcF interval will be explored graphically using a scatter plot. A regression analysis using a linear mixed-effects model will be performed. A plasma LY3154885 concentration-QT analysis will be performed to assess the changes from baseline (Day 1 predose) and time-matched mean placebo in the QTcF interval relative to plasma LY3154885 concentrations across all dose levels. The change from baseline adjustment will be based on individual subject's Day 1 predose value, and an additional placebo adjustment will be based on individual subject's time-matched placebo values. The analysis will be performed by plotting double delta QTcF against LY3154885 concentrations, including all post dosing timepoints. A linear mixed-effects model will be performed on the double delta QTcF values and will include LY3154885 concentration as a covariate. The estimated regression line and associated 90% confidence interval (CI) will be fitted on the plot and the p-value for the slope reported. Estimated delta QTcF and 90% CI at the geometric mean C_{max} (estimated from the highest given dose in the study) will also be presented.

9.5.5.2 Electrocardiogram analysis (Part C)

The same analysis to Part A will be performed in Part C, but the change from baseline adjustment will be based on individual subject's Day 1 predose value, and an additional placebo adjustment will be based on mean time-matched placebo values.

9.5.6 Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) will be performed in all parts of the study. A 24 hours baseline (off study drug) will be measure in all subjects and at least a 2 hour measure prior to dose will be also be measured on selected dosing days. The ABPM device will record ambulatory BP and PR every 30 minutes during awake hours (e. g. 0700 hours to 2200 hours) and every 60 minutes throughout the night (e.g. 2200 hours to 0700 hours).

The primary parameters for the ABPM data will be peak hourly mean values of systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), and nadir hourly mean values for PR. These data will be listed and summarized by part and treatment.

Mean hourly SBP, DBP, MAP, and PR values will be calculated, summarized by part and treatment, and plotted, together with changes from baseline. Baseline value will be defined as the mean value during the 2 hours prior to the planned dosing time.

9.5.7 Neurological Examination

Elements of the neurological examination may include inspection for tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

The below table presents the scoring of the neurological examination findings. For subjects with mild (1+) tremor or nystagmus at baseline, increases in these findings should not be scored at a higher level unless the examiner judges them to be significantly exacerbated compared to baseline.

Score	0	1	2	3	4
Tremor	Absent	Visible with limb extension and/or careful inspection	Visible without limb extension.	Interferes with motor function	
Nystagmus	Absent	1 to 3 beats on lateral gaze	>3 beats on lateral gaze	Present on forward gaze	
Reflexes (brachial or patellar)	Normal	Trace	Absent	Increased	Clonic
Finger-nose	Normal	Abnormal			
Romberg sign	Absent	Present			

The frequency of neurological survey data will be summarized by part, treatment and timepoint, and listed.

9.5.8 Columbia-Suicide Severity Rating Scale (Part C Only)

The Columbia Suicide Severity Rating Scale (C-SSRS) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviours during the assessment period. The C-SSRS and Lilly Self-Harm Supplement Form data will be listed.

9.5.9 Exploratory Scales and Questionnaire (Part C Only)

The Penn Physician Withdrawal Checklist (PWC-20) is a 20-item checklist that will be used to assess the presence and severity of withdrawal symptoms. The PWC-20 data will be summarized by treatment and timepoint and listed.

9.5.10 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥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 subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from

any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment 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 subject data listings.

9.5.11 Other assessments

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

9.5.12 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

Access to safety and tolerability data is scheduled to occur after every dosing session. Pharmacokinetic data will be reviewed to guide implementation of this study and to support dose escalations. Data reviews may be added as deemed appropriate by the sponsor without a protocol amendment.

No 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.

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 subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, “No serious adverse events occurred for this study.”

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