Statistical Analysis Plan I8D-MC-AZEB

Effect of LY3314814 on the Pharmacokinetics of Rosuvastatin in Caucasian Healthy Subjects

NCT03019549

Approval Date: 21-October-2016

STATISTICAL ANALYSIS PLAN

Effect of LY3314814 on the Pharmacokinetics of Rosuvastatin in Caucasian Healthy Subjects

Statistical Analysis Plan Status: Final
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Study Drug: LY3314814

Sponsor Reference: I8D-MC-AZEB
Covance CRU Study: 1000071-8349582

Clinical Phase I

Approval Date: 14-Dec-2016 GMT

1. TABLE OF CONTENTS

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2. ABBREVIATIONS

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

AE	Adverse event
AUC	Area under the concentration versus time curve
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
AUC(0-∞)	Area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AUC_τ	Area under the concentration versus time curve during one dosing interval
BQL	Below the quantifiable lower limit of the assay
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
QD	Once daily
SAP	Statistical Analysis Plan

SD	Standard deviation
SNP	Single nucleotide polymorphism
SOP	Standard Operating Procedure
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{last}	Last time point with a measurable concentration
t_{max}	Time of maximum observed drug concentration
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 21 October 2016).

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 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 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.

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This SAP is written with consideration of the recommendations outlined in the International Council 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 is to evaluate the effect of LY3314814 on the PK of rosuvastatin in healthy subjects.

4.2 Secondary Objectives

The secondary objectives are:

- To assess the safety of LY3314814 when coadministered with rosuvastation in healthy subjects.
- To determine the effect of rosuvastatin on the PK of LY3314814.

4.3 Exploratory Objective

CCI [redacted]

5. STUDY DESIGN

This is a Phase 1, open-label, fixed-sequence, 2-period crossover study to evaluate the PK of rosuvastatin administered alone and after 7 days of treatment with LY3314814 in Caucasian healthy male subjects and female subjects not of c hildbearing potential. Figure 1 illustrates the study design. All subjects will receive each of the following treatments:

Period 1: single oral dose of 20 mg rosuvastatin on Day 1.
Period 2: oral doses of 50 mg LY3314814 once daily (QD) on Days 1 to 12 with a single 20 mg rosuvastatin oral dose coadministered on Day 8.

Period 2 will immediately follow Period 1, with no anticipated break between periods. Subjects will reside at the clinical research unit (CRU) for the duration of both study periods.

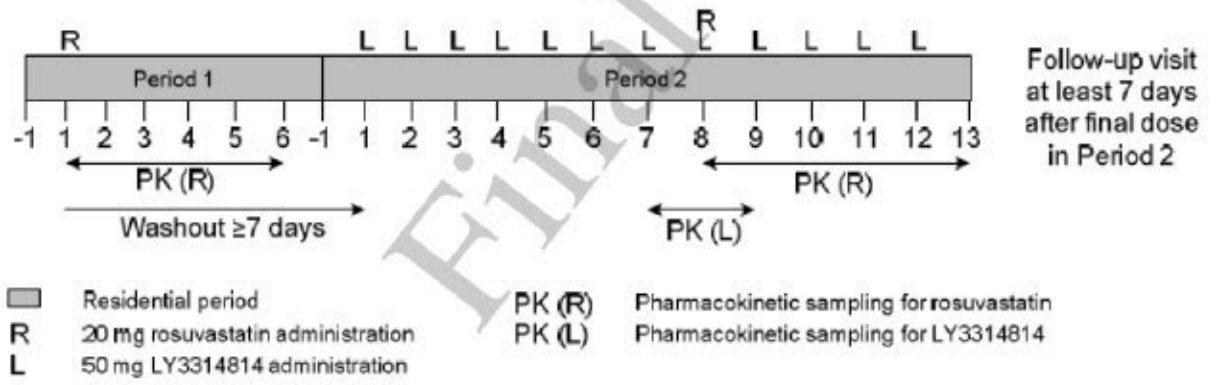

Figure 1. Illustration of study design for Protocol I8D-MC-AZEB

Each subject will provide informed consent for study participation and will undergo a screening examination within 45 days prior to enrollment. Subjects who meet all other screening eligibility criteria will return for a second screening visit, at least 21 days prior to enrollment, when samples will be collected for genotype analysis.

In Period 1, subjects will be admitted to the CRU on Day **-1**. On the morning of Day 1, after an overnight fast of at least 8 hours, a single oral dose of 20 mg rosuvastatin will be administered and will be followed by a fast of at least 4 hours. Blood samples will be collected predose and up to 120 hours postdose (Day 6) for measurement of plasma rosuvastat in concentrations.

There will be a washout period of at least 7 days between the single dose of rosuvastatin on Day 1 in Period 1 and the first dose of LY3314814 on Day 1 in Period 2.

In Period 2, oral doses of 50 mg LY3314814 QD will be taken in the mor ning of Days 1 to 12. On the morning of Day 7, LY3314814 will be administered after an overnight fast of at least

8 hours and followed by a fast of at least 4 hours. On Day 8, after an overnight fast of at least 8 hours, a single oral dose of 20 mg rosuvastatin will be coadministered with 50 mg LY3314814 and will be followed by a fast of at least 4 hours. On Days 7 and 8, blood samples will be collected predose and up to 24 hours after the LY3314814 dose to determine plasma LY3314814 concentrations. Blood samples will be collected predose on Day 8 and up to 120 hours postdose (Day 13) for measurement of plasma rosuvastatin concentrations. Subjects will be discharged on Day 13 of Period 2 after all assessments have been completed. A follow-up visit will occur at least 7 days following the final LY3314814 dose in Period 2.

Safety and tolerability will be assessed throughout the study by means of vital sign measurements, clinical laboratory tests, electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale (C-SSRS), physical examinations (as indicated), and adverse event (AE) recording.

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
20 mg rosuvastatin (D1)	1
50 mg LY3314814 QD (D1 – D7)	2
50 mg LY3314814 QD + 20 mg rosuvastatin (>= D8)	3

D = Day

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

Study Treatment Name	Treatment order in TFL
20 mg rosuvastatin	1
50 mg LY3314814 QD + 20 mg rosuvastatin	2
50 mg LY3314814 QD	3

7. SAMPLE SIZE JUSTIFICATION

Up to 28 subjects may be enrolled in order that 24 subjects complete the study.

For rosuvastatin area under the concentration curve (AUC), the intrasubject variability (coefficient of variation [CV%]) was estimated to be 25.5% by assuming intrasubject variability comprised half of the total variability of 51% (CDER 2003); Martin et al. (2016) estimated the intrasubject variability of rosuvastatin AUC to be 21%. A sample size of 24 subjects will

provide 92.3% probability that the estimated AUC geometric mean ratio will be within 0.15 of the upper and lower bounds of the 90% confidence interval (CI) in the log scale, which corresponds to approximately 0.162 in the natural scale.

While this study is not powered for the maximum observed drug concentration (C_{max}) geometric mean ratio to be within 0.15 of the upper and lower bounds of the 90% CI in the log scale, the C_{max} power calculations are described here to give the expected results context. For rosuvastatin C_{max}, the intrasubject variability was estimated to be 35.9% by assuming intrasubject variability comprised half of the total variability of 71.8% (CDER 2003); Martin et al. (2016) estimated the C_{max} intrasubject variability of rosuvastatin to be 34%. A sample size of 24 subjects will provide 19.6% probability that the estimated C_{max} geometric mean ratio will be within 0.15 of the upper and lower bounds of the 90% CI in the log scale.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The Pk analyses will be conducted on the "Full analysis set". This set includes all data from all subjects who received at least one dose of study drug and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration (t_{max}).

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

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: AUCs and C_{max}) the geometric mean and geometric 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 9.3 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. Furthermore, genotyping data will be summarised and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4.1 or later).

Plasma concentrations of rosuvastatin 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	are under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (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

An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

Plasma concentrations of LY3314814 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
$AUC_{\tau, ss}$	ng.h/mL	area under the concentration versus time curve during one dosing interval at steady state
$C_{max, ss}$	ng/mL	maximum observed drug concentration at steady state
$t_{max, ss}$	h	time of maximum observed drug concentration at steady state
CL_{ss}/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration at steady state

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.

- C_{max} 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}.

- 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 (LLOQ), with at least one of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) 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 $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ 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.

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.

9.3.2 Pharmacokinetic Statistical Inference

Rosuvastatin administered alone (Period 1 Day 1) will represent the reference treatment and rosuvastatin coadministered with LY3314814 will represent the test treatment (Period 2 Day 8) for rosuvastatin PK analysis. PK parameter estim tes will be evaluated to delineate the effects of LY3314814 on rosuvastatin PK.

Log-transformed AUC(0-∞) and C_{max} estimates for rosuvastatin will be analyzed using a linear mixed-effects analysis of variance model with treatment as a fixed effect and subject as a random effect. The ratios of geometric least squares (LS) means (ie, rosuvastatin + LY3314814 to rosuvastatin alone) will be calculated along with the 90% CI for the ratios.

The t_{max} for rosuvastatin will be analyzed using a nonparametric method; median differences of rosuvastatin + LY3314814 to rosuvastatin alone and the 90% CI for the median of differences will be calculated.

Example SAS code:

```
proc mixed data=test covtest alpha=0.1;
   class treatment subject;
   model log_pk = treatment / ddfm=kr alpha=0.1;
   random subject;
   lsmeans treatment / pdiff cl alpha=0.1;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
  ods output covparms=cov;
run;
```

A similar analysis will be performed on the secondary endpoints (LY3314814 AUC_{τ}, C_{max} and t_{max}) to evaluate the effect of rosuvastatin on LY3314814, where LY3314814 administered alone (Period 2 Day 7) will be the reference treatment and LY3314814 coadministered with rosuvastatin will remain the test treatment (Period 2 Day 8). Additional analysis may be conducted if deemed appropriate.

The effect of polymorphisms in genes coding for certain transporters (e.g., ABCG2, ABCB1, ABCC2, SLCO1B3, NTCP, and SLCO2B1) on the magnitude of the interaction between rosuvastatin and LY3314814 may be explored. For each subject, the ratio of rosuvastatin exposures with and without concomitant LY3314814 exposures will be calculated. A graphical analysis of these ratios between subjects with and without single nucleotide polymorphisms (SNPs) of interest is intended. Additional analyses may be conducted as warranted.

CCI [redacted]

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as 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 the first dose. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose. AEs by day of onset will be presented.

All AEs will be listed. Treatment-emergent AEs will be summarized by 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 treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 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 tabulated.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 1016). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry, hematology and urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject 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 Day 1 predose of each period. Figures of mean vital signs and mean

changes from baseline profiles by treatment will be presented by treatment. Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram (ECG)

The ECGs will be performed for safety monitoring purposes and will not be presented.

9.4.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS questionnaire will be listed.

9.4.7 Other assessments

All other safety assessments not detailed in this section will be listed but not sum marized or statistically analysed.

9.4.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

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 b e 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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EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
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TFLs	Tables, Figures, and Listings
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4.1 Primary Objective

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4.2 Secondary Objectives

The secondary objectives are:

- To assess the safety of LY3314814 when coadministered with rosuvastation in healthy subjects.
- To determine the effect of rosuvastatin on the PK of LY3314814.

8 hours and followed by a fast of at least 4 hours. On Day 8, after an overnight fast of at least 8 hours, a single oral dose of 20 mg rosuvastatin will be coadministered with 50 mg LY3314814 and will be followed by a fast of at least 4 hours. On Days 7 and 8, blood samples will be collected predose and up to 24 hours after the LY3314814 dose to determine plasma LY3314814 concentrations. Blood samples will be collected predose on Day 8 and up to 120 hours postdose (Day 13) for measurement of plasma rosuvastatin concentrations. Subjects will be discharged on Day 13 of Period 2 after all assessments have been completed. A follow-up visit will occur at least 7 days following the final LY3314814 dose in Period 2.

Safety and tolerability will be assessed throughout the study by means of vital sign measurements, clinical laboratory tests, electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale (C-SSRS), physical examinations (as indicated), and adverse event (AE) recording.

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50 mg LY3314814 QD (D1 – D7)	2
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D = Day

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

Study Treatment Name	Treatment order in TFL
20 mg rosuvastatin	1
50 mg LY3314814 QD + 20 mg rosuvastatin	2
50 mg LY3314814 QD	3

7. SAMPLE SIZE JUSTIFICATION

Up to 28 subjects may be enrolled in order that 24 subjects complete the study.

For rosuvastatin area under the concentration curve (AUC), the intrasubject variability (coefficient of variation [CV%]) was estimated to be 25.5% by assuming intrasubject variability comprised half of the total variability of 51% (CDER 2003); Martin et al. (2016) estimated the intrasubject variability of rosuvastatin AUC to be 21%. A sample size of 24 subjects will

provide 92.3% probability that the estimated AUC geometric mean ratio will be within 0.15 of the upper and lower bounds of the 90% confidence interval (CI) in the log scale, which corresponds to approximately 0.162 in the natural scale.

While this study is not powered for the maximum observed drug concentration (C_{max}) geometric mean ratio to be within 0.15 of the upper and lower bounds of the 90% CI in the log scale, the C_{max} power calculations are described here to give the expected results context. For rosuvastatin C_{max}, the intrasubject variability was estimated to be 35.9% by assuming intrasubject variability comprised half of the total variability of 71.8% (CDER 2003); Martin et al. (2016) estimated the C_{max} intrasubject variability of rosuvastatin to be 34%. A sample size of 24 subjects will provide 19.6% probability that the estimated C_{max} geometric mean ratio will be within 0.15 of the upper and lower bounds of the 90% CI in the log scale.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The Pk analyses will be conducted on the "Full analysis set". This set includes all data from all subjects who received at least one dose of study drug and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration (t_{max}).

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

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: AUCs and C_{max}) the geometric mean and geometric 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 9.3 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. Furthermore, genotyping data will be summarised and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4.1 or later).

Plasma concentrations of rosuvastatin 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	are under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (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

An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

Plasma concentrations of LY3314814 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
$AUC_{\tau, ss}$	ng.h/mL	area under the concentration versus time curve during one dosing interval at steady state
$C_{max, ss}$	ng/mL	maximum observed drug concentration at steady state
$t_{max, ss}$	h	time of maximum observed drug concentration at steady state
CL_{ss}/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration at steady state

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.

- C_{max} 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}.

- 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 (LLOQ), with at least one of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) 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 $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ 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.

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.

9.3.2 Pharmacokinetic Statistical Inference

Rosuvastatin administered alone (Period 1 Day 1) will represent the reference treatment and rosuvastatin coadministered with LY3314814 will represent the test treatment (Period 2 Day 8) for rosuvastatin PK analysis. PK parameter estim tes will be evaluated to delineate the effects of LY3314814 on rosuvastatin PK.

Log-transformed AUC(0-∞) and C_{max} estimates for rosuvastatin will be analyzed using a linear mixed-effects analysis of variance model with treatment as a fixed effect and subject as a random effect. The ratios of geometric least squares (LS) means (ie, rosuvastatin + LY3314814 to rosuvastatin alone) will be calculated along with the 90% CI for the ratios.

The t_{max} for rosuvastatin will be analyzed using a nonparametric method; median differences of rosuvastatin + LY3314814 to rosuvastatin alone and the 90% CI for the median of differences will be calculated.

Example SAS code:

```
proc mixed data=test covtest alpha=0.1;
   class treatment subject;
   model log_pk = treatment / ddfm=kr alpha=0.1;
   random subject;
   lsmeans treatment / pdiff cl alpha=0.1;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
  ods output covparms=cov;
run;
```

A similar analysis will be performed on the secondary endpoints (LY3314814 AUC_{τ}, C_{max} and t_{max}) to evaluate the effect of rosuvastatin on LY3314814, where LY3314814 administered alone (Period 2 Day 7) will be the reference treatment and LY3314814 coadministered with rosuvastatin will remain the test treatment (Period 2 Day 8). Additional analysis may be conducted if deemed appropriate.

changes from baseline profiles by treatment will be presented by treatment. Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram (ECG)

The ECGs will be performed for safety monitoring purposes and will not be presented.

9.4.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS questionnaire will be listed.

9.4.7 Other assessments

All other safety assessments not detailed in this section will be listed but not sum marized or statistically analysed.

9.4.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

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 b e 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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