Statistical Analysis Plan

Title: Pharmacokinetics of LY3298176 Following Administration to Subjects with Impaired Renal Function

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STATISTICAL ANALYSIS PLAN

Pharmacokinetics of LY3298176 Following Administration to Subjects with Impaired Renal Function

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Study Drug: LY3298176

Sponsor Reference: I8F-MC-GPGG
Covance CRU Study: 1000071-8378513

Clinical Phase I

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2. ABBREVIATIONS

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

%AUC(tlast-∞)	percentage of AUC(0-∞) extrapolated
AE	adverse event
ADA	antidrug antibodies
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BMI	body mass index
BQL	below the lower limit of quantification
CL/F	apparent total body clearance of drug calculated after extravascular administration
C_{last}	last quantifiable drug concentration
CLcr	creatinine clearance
C_{max}	maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	coefficient of variation
e.g.	for example (Latin: *exempli gratia*)
EC	Early Clinical
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
ICH	International Council on Harmonisation
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
PK	Pharmacokinetic(s)

SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
T2DM	Type 2 Diabetes Mellitus
TFLs	Tables, Figures, and Listings
$t_{½}$	Half-life associated with the terminal rate constant (λz) in noncompartmental analysis
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal
V_{ss}/F	apparent volume of distribution at steady state after extravascular administration
Vz/F	apparent volume of distribution during the terminal phase after extravascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 15 January 2018).

This SAP describes the planned analysis of the pharmacokinetic (PK) and tolerability 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.

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 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

- To estimate the PK parameters of LY3298176 in subjects with mild, moderate, or severe renal impairment, and in subjects with end-stage renal disease (ESRD) after a single 5-mg subcutaneous (SC) dose of LY3298176 compared to control subjects with normal renal function.

4.2 Secondary Objective

- To assess the tolerability of LY3298176 in subjects with mild, moderate, or severe renal impairment, and in subjects with ESRD after a single 5-mg SC dose of LY3298176 compared to control subjects with normal renal function.

4.3 Exploratory Objective

- To evaluate the formation of antidrug antibodies (ADA) to LY3298176 after a single 5-mg SC dose administered to subjects with mild, moderate, or severe renal impairment, and in subjects with ESRD.

5. STUDY DESIGN

This is a Phase 1, parallel-design, open-label, multicenter, single-dose study to assess PK and tolerability of a single dose of LY3298176 in subjects with mild, moderate, or severe renal impairment, or ESRD, and control subjects with normal renal function. Control Group 1 will be healthy subjects with normal renal function. Subjects with Type 2 Diabetes Mellitus (T2DM) will not be included in Group 1. Subjects with T2DM and renal impairment will be permitted to enroll in Groups 2 to 5, whereas subjects with T2DM and normal renal function will not be permitted. Subjects will be assigned to 1 of 5 groups (Groups 1 to 5) based on criteria outlined in Table 1. Estimated glomerular filtration rate (eGFR) will be determined by the Modification of Diet in Renal Disease (MDRD) abbreviated equation using serum creatinine levels obtained at Screening and on Day -1; subjects will be assigned to groups based on values from Day -1.

The control subjects (Group 1) will be selected in order that the mean and distribution of Group 1 are comparable to the mean and distribution for each group with renal impairment (Groups 2 through 5) for age (± 10 years), sex, race, weight (±10 kg), and body mass index (BMI) (± 20%), as far as is practically possible[3].

Table 1. Subject Groups based on Renal Impairment Status

	Classification	eGFR (mL/min/1.73m^2)
Group 1	Control (normal renal function)	≥90
Group 2	Mild renal impairment	60-89
Group 3	Moderate renal impairment	30-59
Group 4	Severe renal impairment	15-29
Group 5	End-stage renal disease	Requiring dialysis

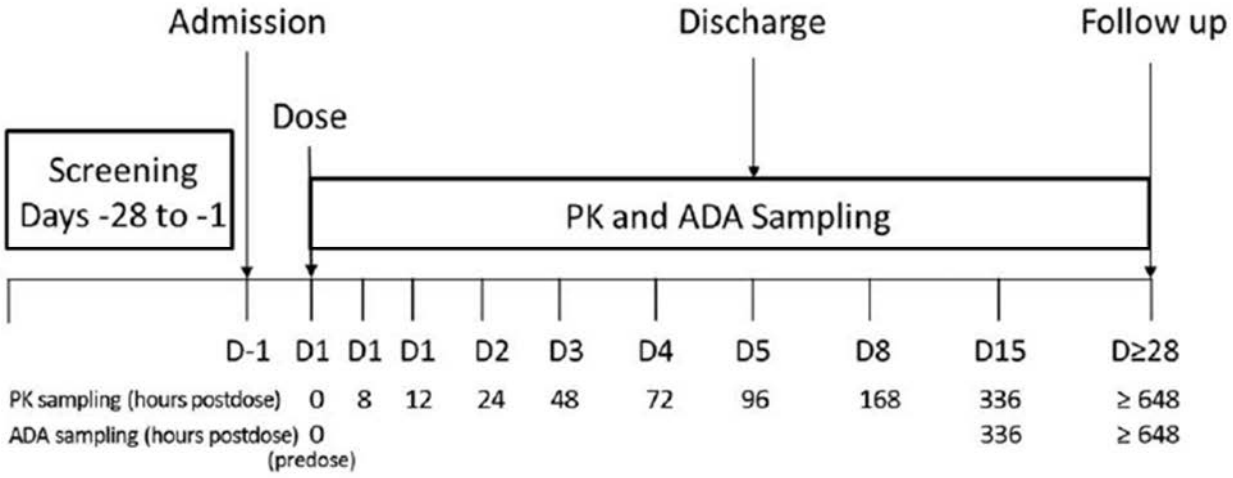
Abbreviations: eGFR = estimated glomerular filtration rate (as determined by the Modification of Diet in Renal Disease abbreviated equation).

Figure 1 and Figure 2 illustrate the study design.

Subjects will visit the Clinical Research Unit (CRU) to sign the informed consent document and undergo screening procedures up to 28 days prior to dosing.

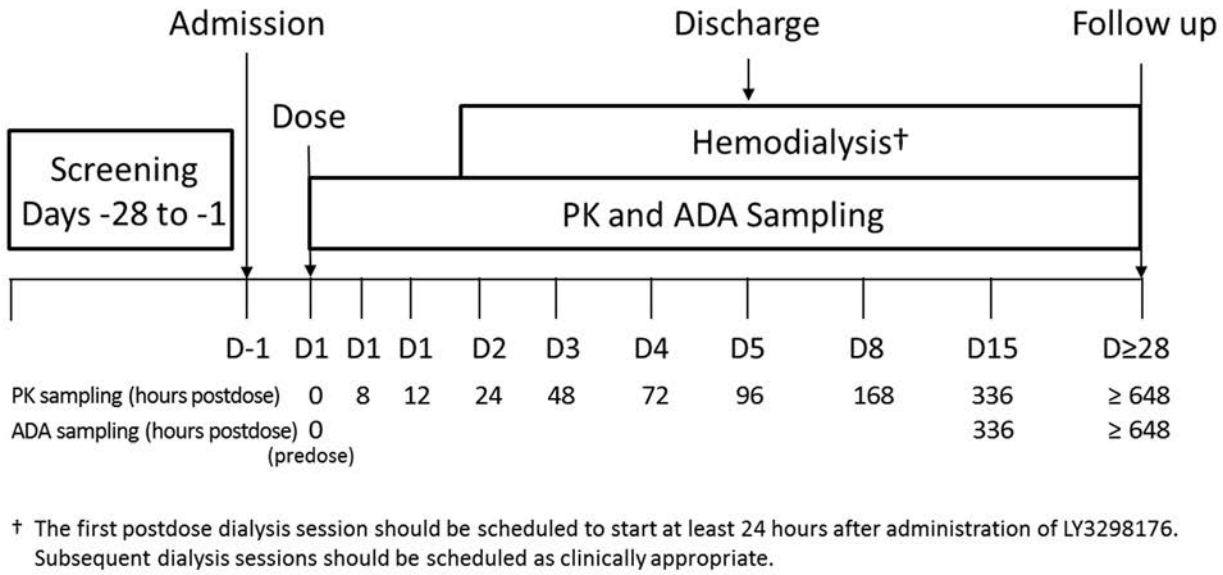
Subjects will be admitted to the CRU on Day -1. Subjects will be administered a single dose of LY3298176 on Day 1 and will remain in the CRU until after assessments are completed on Day 5. Subjects will return for study visits on Days 8 and 15 and for a final follow-up visit at least 28 days postdose.

For subjects with ESRD, administration of LY3298176 should occur at least 24 hours prior to the next planned dialysis session. The time and dates of dialysis sessions from the session immediately prior to dose through Day 8 will be recorded in the case report form (CRF). To eliminate potential variation between different types of dialysis membrane, only high-flux polysulfone membranes will be used.



Abbreviations: ADA = antidrug antibodies; D = Day; PK = pharmacokinetic.

Figure 1. Illustration of study design for Groups 1 to 4.



† The first postdose dialysis session should be scheduled to start at least 24 hours after administration of LY3298176. Subsequent dialysis sessions should be scheduled as clinically appropriate.

Abbreviations: ADA = antidrug antibodies; D = Day; PK = pharmacokinetic.

Figure 2. Illustration of study design for Group 5.

6. TREATMENT

The TFLs will include a subheader for treatment (X mg LY3298176 SC) throughout. The following is a list of group abbreviations that will be used in the TFLs.

Group	Order in TFL
Control (normal renal function)	1
Mild renal impairment	2
Moderate renal impairment	3
Severe renal impairment	4
End-stage renal disease	5

7. SAMPLE SIZE JUSTIFICATION

Approximately 58 subjects will be enrolled so that approximately 48 subjects complete the study, such that approximately 8 subjects per group complete Groups 2 through 5. Approximately 16 completers are needed from Group 1 in order to facilitate demographic matching with the subjects in other groups.

The sample size is not selected to satisfy an a priori statistical requirement. However, the sample size (16 subjects for the control group and 8 subjects per group for the other groups) will provide a 90% coverage probability of the half-width of the 90% confidence interval within 0.29 on a log-scale for comparison of each group to the control group for the area under the concentration versus time curve (AUC) or maximum observed drug concentration (C_{max}), assuming the variability (coefficient of variation [CV]) is 32%. In the natural scale, assuming the ratio is r, the 90% confidence interval for the ratio should be within (0.74r, 1.34r).

Subjects who are enrolled but not administered treatment may be replaced to ensure that a sufficient number of subjects complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The “Pharmacokinetic” population will consist of all subjects who received at least one dose of study drug 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: 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 subject's 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, site ID, body weight, height, BMI, and eGFR will be summarized by group and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using noncompartmental methods in the validated software program, Phoenix WinNonlin (Certara, Version 6.4 or later).

Plasma concentrations of LY3298176 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(t_{last}-∞)	%	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in noncompartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extravascular administration
V_z/F	L	apparent volume of distribution during the terminal phase after extravascular administration
V_{SS}/F	L	apparent volume of distribution at steady state after extravascular administration

Additional PK parameters may be determined where appropriate. The software and version used for the final analysis will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NONCOMPARTMENTAL 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 predose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than 1 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 3 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. If AUC(0-∞) cannot be determined for all subjects an alternative AUC measure, such as AUC to a fixed time point, may be used in the assessment exposure between dose groups.

- 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. $t_{½}$ 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 the predicted last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of 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 nonendogenous.

    - 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 2 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 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 semilogarithmic 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 predose average concentration for single-dose data from nonendogenous 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 predose sample exceeds all measured concentrations for that individual in the subsequent postdose samples.
- For PK profiles during single dosing of nonendogenous compounds, the concentration in a predose 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≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log-transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ± 3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ± 3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ± 3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and n≥6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only 1 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 Methodology

The main analysis is the evaluation of log-transformed AUC(0-∞), AUC(0-t_{last}), and C_{max} using an analysis of variance model with subject group as a fixed factor. The 90% confidence interval of the ratio between each impaired renal function group versus the control group will be estimated.

Example SAS code:

```
proc mixed data=DATA;
   class group;
   model log_pk = group / ddfm=kr;
   lsmeans group / pdiff cl alpha=0.1;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
run;
```

The above analyses will be conducted twice, using different renal function group assignments (eGFR or creatinine clearance [CLcr] based on Day -1 measurements) (Table 2). The analysis based on CLcr will be exploratory.

Table 2. Renal Function Classification for Primary and Exploratory Analyses

Group	Classification	eGFR (mL/min/1.73m^2)[a]	CLcr (mL/min)[b]
1	Control (normal renal function)	≥90	≥90
2	Mild renal impairment	60-89	60-89
3	Moderate renal impairment	30-59	30-59
4	Severe renal impairment	15-29	15-29
5	End-stage renal disease	Requiring dialysis	Requiring dialysis

Abbreviations: CLcr = creatinine clearance; eGFR = estimated glomerular filtration rate.
[a] Per enrollment classification; eGFR will be calculated using the Modification of Diet in Renal Disease abbreviated equation.
[b] CLcr will be calculated using the Cockcroft-Gault formula (Cockcroft and Gault 1976).

The supporting additional analysis is the evaluation of the relationship between the PK of LY3298176 and mean eGFR, as determined by the MDRD abbreviated equation. Scatter plots of PK parameter versus eGFR will be produced and analyzed using either a mixed-effects linear or a nonlinear regression approach with eGFR as a continuous covariate on PK parameters.

t_{max} will be analyzed using a Wilcoxon rank sum test.

If a dose adjustment after interim is needed, descriptive statistics for the PK parameters will be summarized by dose and subject groups. Dose normalization or other methods may be employed for statistical analyses.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse Events

Where changes in severity of an AE are recorded in the 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 that starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE that occurs postdose or is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by group, 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 group, Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 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 2017). Concomitant medication will be listed.

9.4.3 Clinical Laboratory Parameters

All clinical chemistry, hematology, and urinalysis data will be summarized by parameter and group, and 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 group together with changes from baseline, where baseline is defined as Day 1 predose. Figures of mean vital signs and mean changes-from-baseline profiles will be presented by group.

Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram (ECG)

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

9.4.6 Injection Site Assessment

Injection site assessment data (erythema, induration, categorical pain, pruritus, and edema) will be listed and summarized by group in frequency tables.

9.4.7 Glucose Monitoring and Hyperglycemia/Hypoglycemia Reporting

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual blood glucose value, if measured, will be recorded in the CRF, together with any treatments administered. Each category of hypoglycemic event (defined in Section 9.4.3.1 of the Protocol) will be listed and summarized by group.

Blood glucose levels will be listed for individual patients and summarized by group.

9.4.8 Immunogenicity

Immunogenicity data will be listed and frequency tables will be presented. The frequency of treatment-emergent ADAs will also be calculated. If cross-reactivity with native GLP-1 and GIP or neutralizing antibodies against native GLP-1 and GIP assays are performed, the frequency of each will be reported. Treatment-emergent ADAs are those that are induced or boosted by

exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline or a titer 2-fold greater than the minimum required dilution if no ADAs were detected at baseline.

To show the association of treatment-emergent ADAs with AEs, the frequency of treatment-emergent ADAs will be presented by MedDRA preferred term.

The relationship between the presence of antibodies and the PK parameters may be assessed.

9.4.9 Hepatic Monitoring

If a subject 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.

Each subject's 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 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.

9.4.10 Other Assessments

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

9.4.11 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

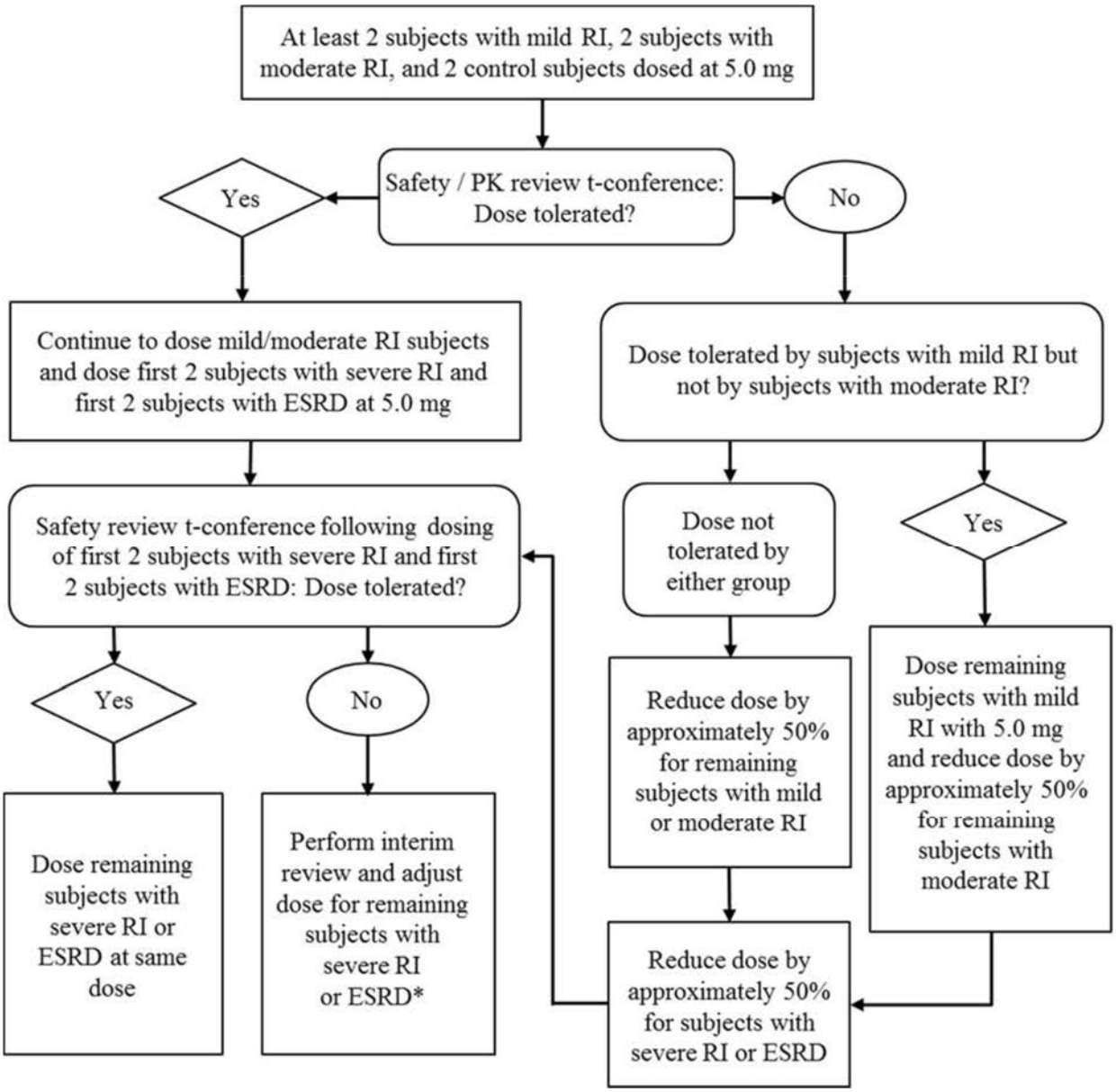
An interim analysis is planned to occur during Study GPGG. Figure 3 illustrates the interim data review decision tree.

Two subjects each from Groups 2 and 3 (subjects with mild and moderate renal impairment, respectively) and Group 1 (appropriate matched-control subjects with normal renal function) will be enrolled in parallel and dosed with 5 mg LY3298176, followed by an interim analysis to evaluate safety, tolerability, and PK data. Based on this interim analysis, a decision will be made about whether or not a dose adjustment is needed, and the study will continue with dosing of the remaining subjects in Groups 2 and 3, along with the first 2 subjects from Groups 4 and 5 (subjects with severe renal impairment and ESRD, respectively) and appropriate matched-control subjects in Group 1. If deemed necessary after dosing of the first 2 subjects in each of Groups 4

and 5 and their appropriate matched-control subjects, a second interim analysis may be performed. Preliminary PK review will be optional for this interim analysis of subjects in Groups 4 and 5. Based on data from the second interim review, a decision will be made regarding dose level. The study will then continue with the remaining subjects with severe renal impairment and ESRD (Groups 4 and 5, respectively) and their applicable matched-control subjects (Group 1).

The purpose of the interim review(s) is to determine the dose level(s) for subsequent subjects. The dose of LY3298176 for subsequent subjects (any or all groups) may be adjusted accordingly after each interim. A reduced dose of approximately 50% is planned, if needed. The final dose determinations will be made by the investigator and the Lilly study team.

If an additional unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, clinical research physician, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.



Abbreviations: ESRD = end-stage renal disease; PK = pharmacokinetic; RI = renal impairment; t-conference = teleconference. *If the subjects with severe RI or ESRD are already being administered a reduced dose, it may be necessary to discontinue enrollment of one or both of these groups.

Figure 3. Interim data review decision tree.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. [FDA] Food and Drug Administration. 2010. Guidance for Industry: Pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labelling.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g., PK parameters) and appropriate summary statistics will be reported to 3 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.”

Leo Document ID = e5f2b0b0-9544-4bd1-bb54-2ff95d05686f

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