Statistical Analysis Plan I8F-JE-GPGC

A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176

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STATISTICAL ANALYSIS PLAN

A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176

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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]).

ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-τ)	Area under the concentration versus time curve during one dosing interval (168 hours)
BQL	Below the lower limit of quantitation
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CRP	Clinical research physician
CRS	Clinical research scientist
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
DPP	Dipeptidyl peptidase
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
HbA1c	hemoglobin A1c
ICH	International Council on Harmonisation
IMP	Investigational medicinal product
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities

MRE	Magnetic resonance elastography
OGTT	Oral glucose tolerance test
PD	Pharmacodynamics
Peak to trough	Ratio of C_{max} to C_{min} (at 168 hours)
PG	Plasma glucose
PK	Pharmacokinetic
QW	Once a week
RA	Accumulation ratio based on AUC(0-τ)
SAE	Serious AE
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SMPG	Self monitored plasma glucose
TBL	Total bilirubin
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
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 24 August 2017).

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 analyses of PK and PD 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 patient 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 AND ENDPOINTS

4.1 Primary Objective

- To investigate the safety and tolerability of LY3298176 after multiple subcutaneous (SC) doses administered to Japanese patients with type 2 diabetes mellitus (T2DM).

  Endpoint: Adverse events (AEs)

4.2 Secondary Objectives

- To characterize the PK of LY3298176 after multiple SC doses in Japanese patients with T2DM.

  Endpoints: Area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}) of LY3298176

- To investigate the PD effect of LY3298176 after multiple SC doses administered to Japanese patients with T2DM.

  Endpoints: Fasting plasma glucose levels

4.3 Exploratory Objectives

- To investigate the exploratory PD effects of LY3298176 after multiple SC doses administered to Japanese patients with T2DM.

  Endpoints: Body weight, oral glucose tolerance test (OGTT) (serum glucose and insulin), 7-point self-monitored plasma glucose (7-p SMPG), hemoglobin A1C (HbA1c), lipids, glucagon, subjective appetite sensation

- To evaluate the impact of formation of antidrug antibodies (ADAs) on LY3298176 after multiple SC doses administered to Japanese patients with T2DM.

  Endpoint: Presence of ADAs to LY3298176

5. STUDY DESIGN

This study is a Phase 1, multiple-site, patient- and investigator-blind, placebo-controlled, randomized, parallel dose–group, 8-week multiple ascending dose (MAD) study in Japanese patients with T2DM.

Figure 1 illustrates the study design.

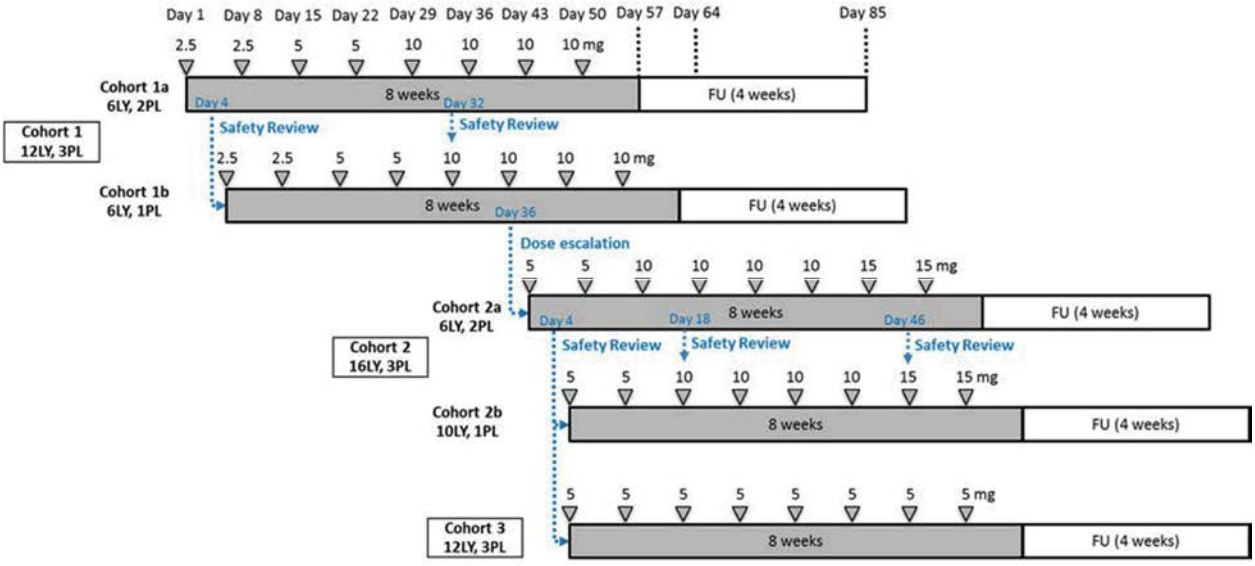

Figure 1. Illustration of study design

This study consists of 3 cohorts. Patients will be randomized to 3 treatment regimens or placebo within each cohort, including up to 3 dose levels of LY3298176 in each regimen, as shown in Figure 1. Patients will be administered 8 weekly SC doses of LY3298176 or placebo.

Screening to Prestudy

Patient eligibility for this study will be determined at a screening visit. Eligible patients will visit the clinical research unit (CRU) before Day -1 to receive training on the 7p-SMPG, glucose meters, test strips, and diaries. Patients will conduct the 7-point SMPG until the day before Day -1. In addition, patients treated with metformin or dipeptidyl peptidase intravenous (DPP-IV) inhibitors (except for omarigliptin, trelagliptin, and linagliptin) will be required to withdraw their treatment and have at least a 28-day washout period before dosing with investigational medicinal product (IMP). These patients will be required to monitor their plasma glucose (PG) levels during the washout period.

Treatment Period

Patients will be admitted to the CRU on Day -1. If the investigator decides not to administer the first dose to a patient on a particular day based on the results of medical assessments, vital signs, or electrocardiograms (ECGs), the patient may be rescheduled to participate in the study, and any procedures performed up to that point may be repeated.

Patients will be given SC doses of LY3298176 (or placebo) on Days 1, 8, 15, 22, 29, 36, 43, and 50 after an overnight fast (at least 8 hours). Even if there are visit allowances of ±1 day, the interval of each IMP administration must be at least 6 days.

Patients in Cohort 1 will receive either LY3298176 with titration regimen starting from 2.5 mg for Days 1 and 8 followed by 5 mg for Days 15 and 22, and 10 mg for Days 29, 36, 43, and 50, or corresponding volume-matched placebo. Patients in Cohort 2 will receive either LY3298176 with titration regimen starting from 5 mg for Days 1 and 8 followed by 10 mg for Days 15, 22, 29, and 36, and 15 mg for Days 43 and 50, or corresponding volume-matched placebo. Patients in Cohort 3 will receive either 5 mg LY3298176 or placebo for 8 weeks. The planned highest dose or dosing regimen of Cohort 2 may be changed for the reason of tolerability.

If the investigator decides not to up-titrate the dose level of IMP for individual patients in the titration regimen in Cohorts 1 or 2 for the reason of safety and/or tolerability, patients may keep current dose level to the planned last dose at Day 50 and will no longer be allowed up-titration during the treatment period. Down-titration is not allowed during the treatment period for any patients in Cohorts 1, 2, or 3.

Safety, as assessed by AEs, vital signs, 12-lead ECGs, concomitant medications, safety laboratory measurements, and medical assessments from at least 8 patients (to include at least 5 on LY3298176) up to Day 36 predose procedure of Cohort 1, will be reviewed by the sponsor and investigator before dose-escalation decision to Cohort 2.

Dosing will be staggered in Cohorts 1 and 2 so that an initial group of up to 6 patients receiving LY3298176 and 2 patients receiving placebo will be dosed. On Days 4 and 32 of Cohort 1 and on Days 4, 18, and 46 of Cohort 2, the investigator and Lilly clinical pharmacologist, clinical research physician (CRP), or clinical research scientist (CRS) will review available safety data from these patients, and if no relevant safety signals are noted, the remaining patients will be dosed. Patients in Cohort 3 will be dosed after evaluation of safety data of the initial staggered group of Cohort 2.

PK sampling and safety assessments, including AEs,/concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, will be performed according to the Schedule of Activities.

The investigator or qualified designee will review all available inpatient safety data before discharging patients from the CRU on the morning of each planned discharging day provided they are deemed medically fit by the investigator. Patients may be required to remain at the CRU longer than the planned discharging day at the investigator's discretion to assure patients' safety or to provide additional safety monitoring. Patients will be discharged after the review of all final safety assessments from the last follow-up visit is completed by the investigator.

Follow-Up Period

Safety follow-up visits will occur approximately 2 and 5 weeks after the last dose of IMP. Patients who have treatment-emergent LY3298176 ADAs at the planned follow-up visit (Day 85) or early termination visit may be monitored until return to baseline.

6. TREATMENTS

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

Cohort	Study Treatment Name	Treatment order in TFL
1-3	Placebo	1
1	2.5 mg LY3298176	2
	5 mg LY3298176	3
	10 mg LY3298176	4
2	5 mg LY3298176	5
	10 mg LY3298176	6
	15 mg LY3298176	7
3	5 mg LY3298176	8

The treatment regimens used will be**:**

Study Treatment Regimen	Treatment order in TFL
Placebo QW	1
2.5 mg – 10 mg LY3298176 QW	2
5 mg – 15 mg LY3298176 QW	3
5 mg LY3298176 QW	4

7. SAMPLE SIZE JUSTIFICATION

The sample size for the study was chosen to provide sufficient data to evaluate the primary objective of this study and is not intended to achieve any a priori statistical requirements.

Approximately 49 Japanese patients with T2DM may be enrolled so that approximately 32 patients complete the study with compliant defined dosing regimen. The estimated drop-out rates are 30% for Cohorts 1 and 3 and 50% for Cohort 2. Patients will be administered 8 weekly SC doses of LY3298176 or placebo in a ratio of 12 LY3298176 : 3 placebo for Cohorts 1 and 3, and 16 LY3298176 : 3 placebo for Cohort 2. Considering the possibility of higher drop-out rate when administered the highest dose level of LY3298176, the number of patients to be enrolled in Cohort 2 is higher than those for the other 2 cohorts.

Replacement of discontinued patients is not planned because the sample size is determined considering the expected drop-out rate.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The “Pharmacokinetic” population will consist of all patients who received at least one dose of IMP and have evaluable PK data.

The “Pharmacodynamic” population will consist of all patients who received at least one dose of IMP and have evaluable PD data.

Patients treated with placebo will be pooled for PD and safety analyses.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients are assigned to analysis populations.

Additional analyses will be conducted on the basis of the treatment groups defined by titration regimen as actually treated, if deemed necessary, after data review.

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 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 patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for patients 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 patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient'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 Patient Disposition

Patient disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height, body mass index, screening HbA1c levels, fasting plasma glucose (Day 1, Predose for each cohort), duration of diabetes, and baseline vital signs (pulse rate and blood pressure, Day -1 for each cohort) will be summarized by treatment regimen, and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Model-based analysis will be performed combined with data from other studies by Global PK/PD and Pharmacometrics group in Eli Lilly and Company. Details will be described in a separate analysis plan.

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin 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-τ)	ng.h/mL	area under the concentration versus time curve during one dosing interval (e.g. 168 hours)
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{½}$	h	half-life associated with the terminal rate constant (λ_z) in non compartmental analysis (Week 8 dose only)
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 (Week 8 dose only)
RA	n/a	accumulation ratio based on AUC(0-τ)
Peak to trough	n/a	ratio of C_{max} to C_{min} (at 168 hours)

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 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- $t_{½}$ 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 patient 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 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 patient or from a subsequent dose period following a suitable wash-out period.
    - The timepoints occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

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 timepoint 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:

- During the terminal elimination phase, the concentration is quantifiable and follows 2 consecutive concentrations that are BQL.
- 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. A value within an individual profile, (e.g. plasma concentrations obtained at the same point in identically treated individuals), may be excluded from analysis if it falls outside the range of acceptable values calculated as described in the methods below.

2. 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.

3. 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 Methodology

PK parameters will be summarized using descriptive statistics by dose level.

PK dose proportionality may be assessed in an exploratory manner in model-based analysis performed by Eli Lilly.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

The ability of LY3298176 to reduce fasting or dynamic glucose and the effects on insulin will be assessed. Such effects will be explored for different treatment regimens of LY3298176.

The following data will be summarized by treatment regimen and day, and listed:

- Fasting glucose concentrations
- Glucose concentrations and AUC(0-2h) during OGTT
- Insulin concentrations and AUC(0-2h) during OGTT
- Lipid panel (including high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglycerides)
- Adiponectin concentrations (if available)
- Blood urea nitrogen concentrations
- Cortisol concentrations (if available)

- HbA1c concentrations
- 7-point glucose profile
- Markers of bone metabolism (if available)
- Meal intake and subjective rating of appetite sensation

The AUC(0-2h) for glucose and insulin during an OGTT will be calculated using the trapezoidal rule. The AUC(0-2h) as well as other derived parameters or observed concentration at specific timepoints for each patient on the study day will also be baseline-adjusted. The concentrations on Day 1, predose will be used as baseline.

9.4.2 Pharmacodynamic Statistical Methodology

Statistical inference on PD parameters (fasting blood glucose, OGTT glucose, and insulin) will be based on the patients who are included in the PD population. PD parameters may be transformed before statistical analyses, if deemed necessary.

The observed results, as well as change from baseline, will be analyzed by treatment regimen, using mixed-effects models to evaluate treatment effects, as well as treatment comparisons. The model will include treatment regimen actually received, as a fixed effect and the patient as a random effect. For repeated measured parameters, day and treatment regimen-by-day interaction terms will be included in the model. Baseline (Day -1) values, as well as other influencing variables, may be used as covariates. An unstructured covariance structure will be applied. If the model fails to converge, alternative structures shall be examined using Akike's criteria. The main comparisons will be between each LY3298176-treated group and placebo group. Least-squares means as well as 95% CIs will be reported.

Example SAS code for repeated measures analysis:

```
proc mixed data=pd;
   class subject trtreg day;
   model chg = base trtreg day trtreg*day / residual ddfm=kr;
   repeated day / subject=subject type=un;
   lsmeans trtreg / alpha=0.05 cl pdiff;
   ods output lsmeans=lsm;
   ods output diffs=diff;
run;
```

where 'chg' is the change from baseline, 'base' is the baseline value, and 'trtreg' is the treatment regimen.

Example SAS code for mixed-effects analysis:

```
proc mixed data=pd;
   class subject trtreg;
   model pd = trtreg / residual ddfm=kr;
   random subject;
   lsmeans trtreg / alpha=0.05 cl pdiff;
   ods output lsmeans=lsm;
   ods output diffs=diff;
run;
```

where 'trtreg' is the treatment regimen.

The individual observed and mean (SD) time profile of the postdose PD parameters will be plotted by treatment regimen. Additional exploratory analyses of PD parameters may be performed to understand dose response using relevant model considering titration scheme, as deemed appropriate.

9.4.3 Pharmacokinetic/Pharmacodynamic Analyses

PK/PD modeling may be used to characterize the exposure-response relationships between LY3298176 concentrations and various PD and key safety endpoints, provided data are sufficient, and will be reported separately.

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 patient has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE (TEAE) is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose. AEs will also be presented by day of onset.

All AEs will be listed. TEAEs will be summarized by treatment regimen, severity, and relationship to the study drug. The frequency (the number of AEs, the number of patients experiencing an AE and the percentage of patients experiencing an AE) of TEAEs will be summarized by treatment regimen, Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 system organ class, and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2017 Enhanced Dictionary B2 Format). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by treatment regimen and parameter together with changes from baseline, where baseline is defined as Day -1, and listed. 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 patient data listings.

9.5.4 Vital signs

Vital signs data will be summarized by treatment regimen 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 treatment regimen. Furthermore, values for individual patients will be listed.

For change from baseline in vital signs, a mixed-model repeated-measure model with treatment regimen, time (of measurement), and treatment regimen-by-time interaction as fixed effects, patient as random effect, and baseline as covariate will be used to determine the effects of LY3298176. An unstructured covariance structure will be applied. If the model fails to converge, alternative structures shall be examined using Akike's criteria. Least-squares means, as well as 95% CIs, will be reported.

Example SAS code:

```
proc mixed data=safety;
   class subject trtreg day;
   model chg=trtreg day trtreg*day base / residual ddfm=kr;
   repeated day / subject=subject type=un;
   lsmeans trtreg*day / alpha=0.05 cl pdiff;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
run;
```

where 'chg' is the change from baseline, 'base' is the baseline value, and 'trtreg' is the treatment regimen.

9.5.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QTcB intervals, QRS duration and heart rate, where QTcB is the QT interval corrected using Bazett's formula. 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 treatment regimen together with changes from baseline, where baseline is defined as the mean of all measurements on Day 1 predose of the treatment period. Figures of mean ECG data and mean changes from baseline will be presented by treatment regimen.

A plasma LY3298176 concentration-QT analysis will be performed to assess the changes from baseline (Day 1 predose) and placebo in the (double delta) QTcF interval relative to plasma LY3298176 concentrations across all active treatments. The change from baseline adjustment will be based on individual subject's Day 1 predose value, and the change from placebo adjustment will be based on the mean of time-matched placebo values.

Further details on how these will be calculated:

- Calculate the arithmetic mean of the triplicate QTcF for each subject at each timepoint and use this in all subsequent calculations below.
- Calculate the change from baseline at each timepoint for each individual subject who received LY3298176.
- Calculate the mean change from baseline across all the placebo subjects at each timepoint.

- For each subject that received LY3298176 at each corresponding timepoint subtract the mean placebo change from their own individual change from baseline.

- BLQ LY3298176 concentration data will be imputed to 50% of the LLOQ for the purposes of the analysis.

The analysis will be performed by plotting double delta QTcF against LY3298176 concentrations, including all post Day 1 dosing timepoints.

A mixed effects analysis model will be performed on the double delta QTcF values and will include LY3298176 concentration as a covariate and subject as a random effect. The results of the model and associated 90% CI will be fitted on the plot and the p-value for the slope reported. Estimated double delta QTcF and 90% CI at the geometric mean C_{max} will also be presented.

Additional analysis to evaluate effects of AE (such as gastrointestinal or hypoglycemia events) QTcF may be performed if deem necessary.

9.5.6 Body weight

Body weight data and changes from baseline (Day 1, predose) will be summarized by treatment regimen, and listed. Figures of mean body weight and mean changes from baseline profiles will be presented by treatment regimen over time.

9.5.7 Hepatic Monitoring

If a patient 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 will be collected if 1 or more of the following conditions occur:

- Elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests

- Elevated serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)

- Elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests

- Patient discontinued from treatment because of a hepatic event or abnormality of liver tests

- Hepatic event considered to be an SAE

The patient'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 (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 regimen, and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data, as well as haptoglobin, will be listed. Values outside the reference ranges will be flagged on the individual patient data listings.

9.5.8 Pancreatic Safety

If a patient experiences elevated serum amylase or lipase values ≥3× ULN, additional monitoring and tests will be performed to confirm the abnormality, even in asymptomatic patients.

All serum amylase and lipase data will be summarized by treatment regimen, and listed.

9.5.9 Hypersensitivity and Injection Site Reactions

Hypersensitivity reaction data will be listed and summarized in frequency tables by treatment regimen, and timepoint.

Injection-site reaction data, including erythema, induration, pain, pruritus, and edema, will also be listed and summarized in frequency tables by treatment regimen, and timepoint .

9.5.10 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 below) will be listed and summarized by treatment regimen.

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

Hyperglycemia and Hypoglycemia

Hyperglycemic events will be reported by the investigator or designated physician who will be responsible for advising the patient on what further actions to take. Hypoglycemic events will be recorded in the CRF, together with any treatments administered.

The main categories of hypoglycemia are as follows:

- **Documented Glucose Alert Level (Level 1):** plasma/serum glucose ≤70 mg/dL (3.9 mmol/L)
    - **Documented symptomatic hypoglycemia:** with typical symptoms of hypoglycemia.
    - **Documented asymptomatic hypoglycemia:** without typical symptoms of hypoglycemia.

- **Documented unspecified hypoglycemia:** with no information about symptoms of hypoglycemia available. (This has also been called unclassifiable hypoglycemia.)

- **Documented Clinically Significant Hypoglycemia (Level 2):** with similar criterion as above except for threshold plasma/serum glucose <54 mg/dL (3.0 mmol/L)
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG <54 mg/dL (3.0 mmol/L)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG <54 mg/dL (3.0 mmol/L)
  - **Unspecified hypoglycaemia:** an event during which PG <54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded

- **Severe Hypoglycemia (Level 3)**
  - **Severe hypoglycemia (in adults):** Patients had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma/serum glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma/serum glucose concentration to normal is considered sufficient evidence that the event was induced by a low plasma/serum concentration (plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]).
  - **Severe hypoglycemia requiring medical attention:** Severe hypoglycemic events when patients require therapy by Health Care Providers (Emergency Medical Technicians, emergency room personnel, etc) are of particular interest to payers. Therefore, some clinical trials may collect data on this subset of severe hypoglycemia episodes, especially if economic outcomes analyses may be based on trial results.

- **Other Hypoglycemia**

    - **Nocturnal hypoglycemia:** Any documented hypoglycemic event (including severe hypoglycemia) that occurs at night and presumably during sleep. At Lilly, this is captured as hypoglycemia that occurs between bedtime and waking. This definition is more useful than the commonly used ~midnight to ~6 AM definition, which does not take patients' individual sleep times into consideration and is consistent with the American Diabetes Association recommendations for reporting events that occur during sleep (American Diabetes Association 2005). It is also important to collect the actual time when a hypoglycemic event occurred to allow further characterization of hypoglycemia timing (e.g., to allow analysis of frequency of events occurring during a 24-hr time period). Nocturnal hypoglycemia may occur at severity Levels 1, 2, or 3.

    - **Relative hypoglycemia (also referred to as pseudohypoglycemia [Seaquist et al. 2013]):** An event during which typical symptoms of hypoglycemia occur, that does not require the assistance of another person, and is accompanied by plasma/serum glucose >70 mg/dL (3.9 mmol/L). The plasma/serum glucose value for patients with chronically poor glycemic control can decrease so rapidly that patients may report symptoms of hypoglycemia before their plasma/serum glucose concentration falls below 70 mg/dL (3.9 mmol/L). Events with plasma/serum glucose ≤70 mg/dL should not be categorized as relative hypoglycemia. Evaluation and statistical analysis of this category is optional. However, if a patient reports a relative hypoglycemia event where assistance from another person was received or the patient experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycemia event and report it appropriately.

    - **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia were present, but plasma/serum glucose measurement was not reported.

    - **Overall (or total) hypoglycemia:** This optional category combines most cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). It does not include relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in the category of overall (or total) hypoglycemia.

9.5.11 Immunogenicity

The frequency of antibody formation (presence and titers) to LY3298176 will be determined. If any cross-reactive or neutralization assays are performed, the frequency of antibodies will be determined. If there are a sufficient number of patients with positive antibodies to LY3298176, the change of antibodies (negative to positive) will be summarized using shift tables.

The relationship between the presence of antibodies, antibody titers, and clinical parameters (e.g., AEs) may be assessed. Likewise, the relationship between antibody titers, LY3298176 concentration (or PK parameters), and PD response to LY3298176 may be assessed.

Furthermore, immunogenicity data will be listed for individual patients.

9.5.12 Other assessments

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

10. INTERIM ANALYSES

Interim analysis may be conducted when all data through Day 85 become available from all cohorts. Additional interim analysis may be conducted to proceed to the subsequent Japan studies. For this purpose, at least safety and PK data may be analyzed.

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 patients 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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