Statistical Analysis Plan

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

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STATISTICAL ANALYSIS PLAN

Single- and Multiple-Ascending Dose Study in Healthy Subjects to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176 and Multiple Doses in Patients with Type 2 Diabetes Mellitus

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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]).

AE	adverse event
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
AUC(0-τ)	area under the concentration versus time curve during one dosing interval
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(t_{last}-∞)	percentage of AUC(0-∞) derived by extrapolation
BQL	below the lower limit of quantitation
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
CRU	Clinical Research Unit
CV	coefficient of variation
EC	Early Clinical
ECG	electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
HbA1c	Hemoglobin A1c
ICH	International Council on Harmonisation
LLOQ	lower limit of quantification
LS	least square
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	Metabolic ratio based on AUC(0-∞)
NA	not applicable
PD	pharmacodynamic

PK	pharmacokinetic
RL	Linearity ratio
SAD	single ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure
SRP	Safety review panel
T2DM	Type 2 diabetes mellitus
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
V_z/F	apparent volume of distribution during the terminal phase after extra-vascular administration
R_A	Accumulation ratio
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 17 February 2016 and amendment (b) dated 23 April 2016).

This SAP describes the planned analysis of the safety, tolerability , pharmacokinetic (PK) and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data . In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first subject administration 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

Primary Objective

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

Secondary Objectives

- To characterize the PK of LY3298176 following SC doses of LY3298176 in healthy subjects and patients with T2DM.
- To investigate the PD effects of LY3298176 following multiple SC doses of LY3298176 administered to healthy subjects.
- To investigate the PD effects of LY3298176 following multiple SC doses of LY3298176 administered to patients with T2DM.

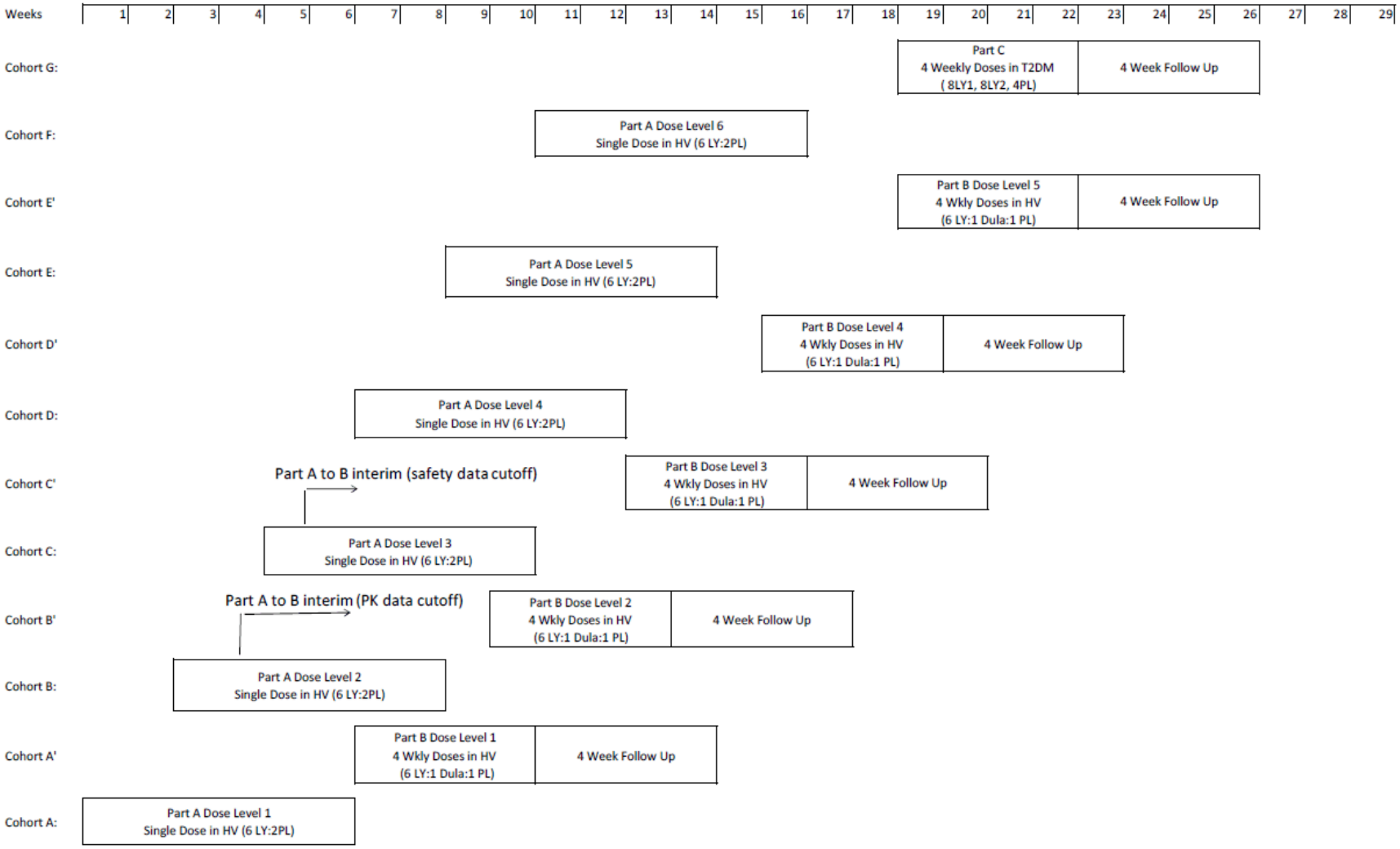
Exploratory Objective

- To investigate LY3298176 effects on markers of bone metabolism (formation and resorption) following multiple SC doses of LY3298176 administered to patients with T2DM.

5. STUDY DESIGN

Study GPGA is a Phase 1, multiple-site, patient-/subject- and investigator-blind, placebo controlled, randomized, parallel-dose group, single-ascending dose (SAD; Part A), and a 4-week multiple-ascending dose (MAD; Part B) study in healthy subjects, and a 4-week multiple-dose evaluation in patients with T2DM (Part C). Part B will evaluate Trulicity® (dulaglutide) as a positive control for PD of GLP-1 pharmacology.

The planned LY3298176 doses for this study range from 0.25 mg up to 10 mg LY3298176. Dulaglutide will be provided as a 1.5-mg SC dose. Figure 1 illustrates the study design.



Abbreviations: Dula=dulaglutide; HV=healthy volunteer; LY=LY3298176; PL=placebo; T2DM=type 2 diabetes mellitus; Wkly=weekly

Figure 1.

Patient/subject eligibility for this study will be determined at a screening visit. Eligible patients/subjects will be admitted to the clinical research unit (CRU) on Day −1 (Part A) or on Day -2 (Parts B and C). Patients/subjects will be given an SC dose of LY3298176 (or placebo or dulaglutide) on Day 1 (Parts A, B, and C) and Days 8, 15, and 22 (Parts B and C only) after an overnight fast (at least 8 hours). PK sampling and safety assessments, including AE, medical assessments, clinical laboratory tests, vital signs, and electrocardiograms (ECGs), will be performed according to the Schedule of Activities. PK or PD sampling schedules may be modified based on the available safety and PK data.

The investigator or qualified designee will review all available inpatient safety data before discharging patients/subjects from the CRU on the morning of Day 4, provided they are deemed medically fit by the investigator. Patients/subjects may be required to remain at the CRU longer than Day 4 at the investigator's discretion. Safety, as assessed by AEs, clinical safety laboratory tests, vital signs, 12-lead ECGs, concomitant medications, and medical assessments, will be reviewed by the sponsor and investigator before each dose-escalation decision.

A Safety Review Panel (SRP) will be established and composed of experts in early phase medicine independent of the study team and investigative site. The SRP will review the evaluation and interpretation of the data from dose escalation safety reviews and protocol-specified interim analyses. Based on that review, the SRP will advise the sponsor and investigator on study conduct.

Patients/subjects will be discharged after the review of all final safety assessments from the last follow-up visit is completed by the investigator.

Single Ascending Dose Study in Healthy Subjects (Part A)
Part A will consist of up to 6 escalating single-dose levels of LY3298176 or placebo in healthy subjects. Approximately 48 subjects will be randomized into 6 groups (Cohorts A through F) as follows:

- Cohorts A through F: 8 subjects per cohort, with a ratio of 6 LY3298176:2 placebo.

Each new dose level will be initiated only if safety results through Day 8 from at least 5 subjects receiving LY3298176 in the preceding dose level are deemed acceptable by the investigator and the Lilly clinical pharmacologist.

Multiple Ascending Dose Study in Healthy Subjects (Part B)
The MAD portion of the study will be initiated after review of safety and PK data from Day 8 of the second SAD dose level and safety data through Day 8 of the third SAD dose level. In Part B, approximately 40 healthy subjects in Cohorts A' through E' will be administered SC doses within the dose and exposure range of the SAD as follows:

- Cohorts A' through E': 8 subjects per cohort, with a ratio of 6 LY3298176:1 placebo:1 dulaglutide.

The dose levels in Part B will be determined on the basis of safety, tolerability, and PK data from Part A. Dose escalations will be based on the evaluation of preliminary safety and tolerability data from at least 5 subjects receiving LY3298176 through Day 15 of the previous MAD dose level. Dose titration scheme may be evaluated pending exposure-response analyses of tolerability data from Part A.

Multiple-Dose Evaluation in Patients with Type 2 Diabetes Mellitus (Part C)
Part C of the study will be a 4 -week multiple-dose evaluation of LY3298176 in approximately 20 patients with T2DM. Patients will be administered SC doses of LY3298176 or placebo in a ratio of 16 LY3298176:4 placebo (Cohort G). Patients receiving LY3298176 may be randomized into 1 of 2 different dose levels (8 patients per dose level). Dose levels will be determined based on safety, tolerability, and PD data from Part B.

Part C may be initiated based on the evaluation of safety and tolera bility data from Part B (MAD).

6. TREATMENTS

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

Part	Study Treatment Name	Treatment order in TFL
A	Placebo	1
	0.25 mg LY3298176	2
	X mg LY3298176	3
	X mg LY3298176	4
	X mg LY3298176	5
	X mg LY3298176	6
	XX mg LY3298176	7
B	Placebo QW	8
	1.5 mg Dulaglutide QW	9
	X mg LY3298176	10
	XX mg LY3298176	11
	XX mg LY3298176	12

	XX mg LY3298176	13
C	Placebo	14
	XX mg LY3298176	15
	XX mg LY3298176	16

Based on safety and tolerability data in Part A, dose-titration regimens may be evaluated in Part B and C. In that case, treatment name will be labeled as "XX-YY-ZZ mg LY3298176".

7. SAMPLE SIZE JUSTIFICATION

For Part A, Cohorts A through F, 6 subjects shall receive LY3298176 and 2 subjects will receive placebo at each dose level. For Part B, Cohorts A' through E', 6 subjects shall receive LY3298176, 1 subject shall receive placebo, and 1 subject shall receive dulaglutide. For Part C, approximately 20 patients with T2DM (16 LY3298176:4 placebo) will complete the 4 weekly SC doses of LY3298176 or placebo.

For each study part, any dropout may be replaced so that the targeted numbers of patients/subjects for safety review and data collection can be achieved. The replacement patient/subject will be assigned to receive the treatment of the dropout.

Up to 110 healthy subjects may be enrolled in Parts A and Part B to achieve the objectives of each part of the study. Up to 25 T2DM patients may be enrolled in Part C to achieve study objectives. The replacement patient/subject will be assigned to receive the treatment of the dropout.

The sample sizes for each part of the study were chosen to provide adequate placebo control for each dosing occasion and are considered sufficient to evaluate the primary objective of this study.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Pharmacokinetic" and Pharmacodynamic" population will consist of all enrolled patients/subjects receiving at least 1 dose of the study drug according to the treatment the patients/subjects actually received. For the calculation of acetaminophen parameters, subjects may be excluded from the summary statistics and statistical analysis if a subject has an adverse event of vomiting that occurs at or before 2 times median t_{max}.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when 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 coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used. An average value will be used if triplicate measures are reported at a single timepoint.

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.

For Part C, baseline hemoglobin A1c (HbA1c) levels (Day 1 predose), fasting blood glucose (Day -1 predose) and baseline vitals (heart rate and blood pressure, Day -1 predose) will also be summarized and listed

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Pharmacokinetic parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.2.1 or later).

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

Part A – LY3298176 PK parameters

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from 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(0-∞) derived by extrapolation
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
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

Part B & C – LY3298176 PK parameters

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 4 only)
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (Week 4 only)
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (Week 4 only)
Peak to trough	n/a	Ratio of C_{max} to C_{min} (e.g.,at 168 hours)
R_A	n/a	Accumulation Ratio based on AUC(0-τ)

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

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. 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.

- 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. For non-bolus, multiple dose profiles, the predose 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 associated with the terminal rate constant ($t_{½}$) 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 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.

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 predose 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 these methods to all pharmacokinetic analyses is not a requirement. Rather, these methods provide justification for exclusion of data when scientifically appropriate. These methods describe the approach 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.

<u>Data within an Individual Profile</u>

A value within an individual profile, (e.g. data collected from a single individual over the time course of single treatment period), 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 below the quantitation limit (BQL).
- For pharmacokinetic profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- For pharmacokinetic profiles during single dosing of non-endogenous 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. 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. 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 Methodology

For the single- and multiple-dose (after multiple dosing only) parts of the study, PK dose proportionality will be assessed separately. Log-transformed C_{max} and AUC(0-∞) for single dose and AUC(0-τ) for multiple dose] of LY3298176 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals (CIs). The estimated ratio of dose-normalized

geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach. The inter-subject coefficient of variation (CV%) will also be derived.

Example SAS code for the analysis:

```
proc mixed data=pk1;
model logvar=logdose / alpha=0.1 cl solution outpred=resids ddfm=kr;
estimate 'xx mg' intercept 1 logdose xx / alpha=0.1 cl; /*Log value of xx*/
estimate 'yy mg' intercept 1 logdose yy / alpha=0.1 cl; /*Log value of yy*/
estimate 'zz mg' intercept 1 logdose zz / alpha=0.1 cl; /*Log value of zz*/
estimate 'zz mg - xx mg' ltrtmnt pp / alpha=0.1 cl; /*Difference in log values
between highest and lowest doses*/
ods output solutionf=est;
ods output estimates=estims;
run;
```

Example SAS code for the derivation of inter-subject CV%:

```
proc mixed data=pk1 covtest alpha=0.1;
class dose;
model logvar=dose / alpha=0.1 cl solution outpred=resids ddfm=kr;
ods output covparms=cov;
run;
```

The parameter T_{max} of LY3298176 will be analyzed using a nonparametric method. A comparison among treatments will be performed using the Kruskal-Wallis test. The P-value will be presented to assess the significance of the treatment comparison.

Example SAS code:

```
proc npar1way data=pk1;
class dose;
var tmax;
run;
```

For Parts A, B, and C, all PK parameters will be summarized using descriptive statistics.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

The pharmacokinetics of acetaminophen will be used as "pharmacodynamics" measure of the effect of LY3298176 on gastric emptying. Plasma concentrations of acetaminophen (Parts B & C only) will be used to determine the following parameters in validated software program (Phoenix WinNonlin Version 6.2.1 or later).:

Part B & C – Acetaminophen parameters

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from 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(0-∞) extrapolated
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

The parameters for acetaminophen will be calculated using the same methodology as PK parameters (Section 9.2.1)

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

- fasting glucose concentrations
- glucose concentrations and AUC(0-2h) during OGTT
- insulin concentrations and AUC(0-2h) during OGTT
- acetaminophen derived parameters
- lipid panel (including high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglycerides)
- adiponectin concentrations
- blood urea nitrogen concentrations
- cortisol concentrations
- hemoglobin A1c concentrations (Part C only)
- 7-point glucose profile (will be summarized by treatment, day and timepoint)
- Markers of bone metabolism

The AUC(0-2h) for glucose and insulin during an OGTT will be calculated using the trapezoidal rule, based on actual timings, on Days -1, 2 and 23. In addition to the AUC, an incremental AUC (subtracting time 0 value) will be calculated. The AUC and incremental AUC on Day -1 will be used as baseline for statistical analysis of change from baseline and placebo. Baseline corrected AUC(0-2h) will also be calculated, where the Day -1 AUC is the baseline AUC.

9.4.2 Pharmacodynamic Statistical Methodology

The PD parameters from each part of the study will be analyzed separately. PD parameters from placebo-treated patients/subjects within each part of the study will be pooled for the final analysis. PD parameters may be transformed before statistical analyses, if deemed necessary. Absolute values as well as change from baseline AUC(0-2h) for glucose and insulin will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The model will include treatment, day, and treatment-by-day interaction as fixed effects and patient/subject as a random effect. Baseline (e.g., Day −1) values, as well as other influencing variables, may be used as covariates. The main comparisons will be between each LY3298176-treated group and placebo group.

Baseline-adjusted C_{max} and AUC0-t_{last} of acetaminophen (ratio to Day -1 value) will be calculated and log-transformed to compare the gastric emptying effect of LY3298176 to that of dulaglutide. A repeated measures analysis with treatment, day, and treatment-by-day interaction as fixed effects, and log baseline (Day -1) as covariate will be used to perform the analysis. Least-squares means as well as 95% CIs will be reported.

Example SAS code:

```
proc mixed data=PD;
class subject day treatment;
model change = baseline subject treatment day treatment*day / ddfm=kr;
repeated day / subject=subject ;
lsmeans treatment*day / pdiff=control cl alpha=0.05;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

Comparisons between the Day 23 dose level and the lowest dose level within a Part will be performed.

The parameter t_{max} of acetaminophen will be analyzed using a nonparametric method using the SAS procedure PROC UNIVARIATE. The treatment medians, median of difference and approximate 90% CI for the median of difference will be presented.

All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment group and day. Summary statistics will be provided.

The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

9.4.3 Pharmacokinetic/Pharmacodynamic Statistical Methodology

Exposure-response analyses of key safety and pharmacology parameters will be performed as the responsibility of Lilly.

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 adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose. Adverse events by day of onset will be presented (for Parts B and C).

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 adverse events, the number of subjects experiencing an adverse event and the percentage of subjects experiencing an adverse event) of treatment-emergent adverse events will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 system organ class and preferred term. The summary and frequency adverse event tables will be presented for all causalities and those considered related to the study drug. Any serious adverse events will be tabulated.

For each part of the study, incidence rates of gastrointestinal AEs (anything within the gastrointestinal System Organ Class) will be summarized and plotted in a histogram showing all treatments.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version Sept 2015). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

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

9.5.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose. 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.

For change from baseline values, a repeated measures model with treatment, time (of measurement), and treatment-by-time interaction as fixed effects, and baseline as covariate will

be used to determine the effects of LY3298176 compared with placebo. Least-squares means as well as 95% CIs for the difference of LY3298176 compared with placebo will be reported. The mean of triplicate measurements at each time point will be used for summary and analysis.

In addition, the time-average of the 0 to 168hr change from baseline data (calculate AUC(0-168) divided by the time interval) will be calculated and this will be analyzed in a mixed effects model with treatment as a fixed effect and subject as a random effect. Least-squares means as well as 95% CIs for the difference of LY3298176 compared with placebo will be reported.

A plasma LY329817 concentration-vital signs analysis will be performed to assess the changes from baseline (Day 1 predose) and placebo in the (double delta) heart rate and blood pressure relative to plasma LY329817 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 change from baseline at each timepoint for each individual subject who received LY329817.
- Calculate the mean change from baseline across all the placebo subjects at each timepoint.
- For each subject that received LY329817 at each corresponding timepoint subtract the mean placebo change from their own individual change from baseline.
- BLQ LY329817 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 heart rate or blood pressure against LY329817 concentrations, including all post Day 1 dosing timepoints. The plot will be produced separately for Parts A, B and C.

A mixed effects analysis model will be performed on the double delta values and will include LY2922470 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 heart rate and blood pressure and 90% CI at the geometric mean C_{max} will also be presented.

9.5.5 Electrocardiogram (ECG)

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

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

The ECG data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

A plasma LY329817 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 LY329817 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 LY329817.
- Calculate the mean change from baseline across all the placebo subjects at each timepoint.
- For each subject that received LY329817 at each corresponding timepoint subtract the mean placebo change from their own individual change from baseline.
- BLQ LY329817 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 LY329817 concentrations, including all post Day 1 dosing timepoints. The plot will be produced separately for Parts A, B and C.

A mixed effects analysis model will be performed on the double delta QTcF values and will include LY2922470 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 listed and summarized.

For change from baseline body weight values in parts B and C, a repeated measures model with treatment, time (of measurement), and treatment-by-time interaction as fixed effects, and

baseline as covariate will be used to determine the effects of LY3298176 compared with placebo on body weight. Least-squares means as well as 95% CIs will be reported. The analysis will be performed separately for Part B healthy subjects and Part C T2DM, comparing LY3298176 and placebo within a part.

9.5.7 Bone Markers

To investigate the effects of LY3298176 on bone metabolism (absorption and resorption) following multiple doses in T2DM (Part C), the following biomarkers will be assessed:

- Serum carboxy-terminal telopeptide fragments of Type I collagen (CTX-1)
- N-terminal propeptide of Type I collagen (P1NP)
- Osteocalcin.

The parameters will be summarized by treatment and day and listed.

9.5.8 Immunogenicity data

Immunogenicity data will be listed and the frequency of positive results will be summarized by day and treatment. The relationship between LY3298176 concentration (or PK parameter) and antibody titre may be explored graphically.

9.5.9 Other assessments

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

Exposure-response analyses of safety parameters, including adverse events (nausea/vomiting) may be performed as the responsibility of Lilly.

10. INTERIM ANALYSES

The Lilly sponsor team is unblinded. Data may be analyzed while the trial is ongoing. An assessment committee will not be formed.

Access to the data is scheduled to occur after every dosing session. The purpose of these reviews is to review the safety data for the next dosing session. The investigator and the Lilly sponsor team will make the determination regarding dose escalation based upon their review of the safety and tolerability data. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

The first interim analysis supporting initiation of the MAD portion of the study (Part B) will be based on review of safety and PK data from Day 8 of the second SAD dose level and safety data through Day 8 of the third SAD dose level. These data may be used to update PK sampling times and dose selection for the remaining cohorts. The second interim analysis supporting initiation of Part C will be based on available data from Part B (MAD).

The third interim analysis will include listings through Day 29 of the highest MAD dose level (Part B) and Day 29 of the T2DM cohort (Part C), excluding ADA assessment. The data will include but are not limited to safety, PK of LY3298176 and acetaminophen (Parts B and C only), and OGTT (Parts B and C only).

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 Pri nciples for Clinical Trials (E9), 5 February 1998.

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

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

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