Statistical Analysis Plan I8F-MC-GPGE

Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of LY3298176 in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

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Study Drug: LY3298176

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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 antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-72)	area under the concentration versus time curve from time zero to 72 hours postdose
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_{τ}	Area under the concentration versus time curve during one dosing interval
BQL	Below the lower limit of quantitation
CI	Confidence interval
CL	Total body clearance of drug calculated after intravenous administration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last observed quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
F	Absolute bioavailability (based upon geometric mean)

GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
ICH	International Council on Harmonisation
IV	Intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TBL	Total bilirubin
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
VAS	Visual Analog Scale
V_{SS}	Volume of distribution at steady state following intravenous administration
V_{SS}/F	Apparent volume of distribution at steady state following extra-vascular administration
V_z	Volume of distribution during the terminal phase after intravenous administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 01 September 2017).

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

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

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 Part A

Primary Objective

To evaluate the PK of a single subcutaneous (SC) dose of LY3298176, administered as solution formulation (test) versus lyophilized formulation (reference) in healthy subjects.

Secondary Objective

To investigate the safety and tolerability of LY3298176, administered to healthy subjects.

4.2 Part B

Primary Objective

To evaluate the PK of a single intravenous (IV) dose of LY3298176 in healthy subjects.

Secondary Objective

To investigate the safety and tolerability of LY3298176, administered to healthy subjects via IV formulation

4.3 Part C

Primary Objective

To evaluate the safety and tolerability of LY3298176, following multiple SC weekly doses of a solution formulation administered in healthy subjects.

Secondary Objective

To evaluate the PK of LY3298176, administered as a solution formulation.

5. STUDY DESIGN

Study I8F-MC-GPGE (GPGE) is a single-center, Phase 1 study conducted in healthy subjects in 3 parts: Part A is a 2-period, 2-treatment, crossover design evaluating the relative bioavailability of 2 formulations of LY3298176; Part B, a single-arm design evaluating LY3298176 PK with IV administration; and Part C is a placebo-controlled, single-arm design evaluating the safety, tolerability, and PK of LY3298176 titrated, once-weekly for 4 weeks.

5.1 Part A

Part A is a randomized, 2-period, crossover study in healthy subjects to evaluate the relative bioavailability of 5 mg LY3298176, administered as a solution formulation (test), compared to a 5-mg dose administered as lyophilized formulation (reference).

Each subject will provide informed consent for study participation, and will undergo a screening examination within 28 days prior to enrollment.

In each treatment period, subjects will be admitted to the clinical research unit (CRU) on Day -1. On the morning of Day 1, following an overnight fast of at least 8 hours, subjects will receive a single SC dose of LY3298176, administered according to their assigned treatment sequences. Blood samples will be collected predose and up to 480 hours postdose to measure LY3298176 concentrations. At a minimum, subjects will remain in the CRU for 8 days. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on the morning of Day 8, provided that the subjects are deemed medically fit.

Subjects may be required to remain in the CRU longer than Day 8, at the investigator's discretion. The subjects will return to the CRU for follow-up visits on Days 21 and 35.

There will be a washout period of at least 35 days between doses in Periods 1 and 2. Based on the PK properties of LY3298176 (terminal half-life: approximately 5 days), a washout period of at least 35 days between doses in Periods 1 and 2 is considered adequate. Period 2 will repeat

the same schedule as Period 1 with the Day 35 visit being the final study visit, which will include an antidrug antibody (ADA) sample at least 10 weeks after the first dose.

5.2 Part B

Part B is a single, 0.5-mg IV dose of LY3298176 solution formulation (or lyophilized formulation in absence of solution formulation) administered to healthy subjects.

Each subject will provide informed consent for study participation, and will undergo a screening examination within 28 days prior to enrollment.

Subjects will be admitted to the CRU on Day -1. On the morning of Day 1, following an overnight fast of at least 8 hours, 2 subjects will receive a single IV dose of 0.5 mg LY3298176, administered over 10 minutes. This dose is expected to be safe while also providing plasma concentrations that can be adequately measured over the course of the sampling time period to enable adequate characterization of the PK profile.

- If the dose of 0.5 mg is found to be safe and well-tolerated, then a PK interim analysis will be performed. Based on the results of the interim analysis, if it is noted that LY3298176 concentrations can be adequately quantified, then 4 more subjects will be dosed.
- If the dose of 0.5 mg is found to be safe and well-tolerated, then a PK interim analysis will be performed. Based on the results of the interim analysis, if it is noted that LY3298176 concentrations cannot be adequately quantified, then a dose adjustment (however less than 1 mg) may be considered for an additional 6 subjects.
- If the dose is not tolerated due to extensive gastrointestinal (GI) events, a lower dose of 0.25 mg (infused over 10 minutes) may be administered to an additional 6 subjects.

Plasma samples will be collected multiple times, including predose and up to 336 hours postdose, to measure LY3298176 concentrations.

At a minimum, subjects will remain in the CRU for 8 days. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on the morning of Day 8, provided that the subjects are deemed medically fit. Subjects may be required to remain in the CRU longer than Day 8, at the investigator's discretion.

Each subject will be required to return to the CRU for a follow-up visit at least 35 days after the LY3298176 dose. In addition, subjects will need to attend a study visit on Day ≥70 for an ADA follow-up sample.

5.3 Part C

Part C is a randomized, titration study where healthy subjects will be assigned LY3298176 or placebo at a ratio of 3 LY subjects to 1 placebo subjects. The investigator and subject will be blinded to the treatment.

Subjects will receive a treatment regimen of either LY3298176 or placebo to be given as a SC dose on Days 1, 8, 15, and 22, after an overnight fast (at least 8 hours). Subjects randomized to

LY3298176 will receive a 5 mg dose on Day 1 and Day 8, a 7.5 mg dose on Day 15, and a 10 mg dose on Day 22, administered via solution formulation.

Each subject will be required to return to the CRU for outpatient visits and for a follow-up visit on Day ≥92.

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	5 mg LY3298176 SC (lyophilized)	1
	5 mg LY3298176 SC (solution)	2
B	0.5 mg LY3298176 IV	3
C	Placebo SC	4
	5-10 mg LY3298176 SC[1]	5

[1] Subjects receive 5 mg LY3298176 SC on Day 1 and Day 8, 7.5 mg LY3298176 SC on Day 15, and 10 mg LY3298176 SC Day 22

7. SAMPLE SIZE JUSTIFICATION

Approximately 20 healthy subjects may be enrolled in Part A in order that at least 16 subjects complete Part A. Up to 10 subjects will be enrolled in Part B in order that at least 6 subjects complete Part B. Approximately 16 healthy subjects may be enrolled in Part C in order that at least 12 subjects complete Part C (in a 3:1 ratio of LY3298176:placebo).

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

7.1 Part A

Assuming the intra-subject variability (coefficient of variation [CV]) is 30%. Based on this assumption, 16 subjects will provide a precision of 0.227 on a log-scale for the area under the concentration versus time curve (AUC) or the maximum observed drug concentration (C_{max}) with 90% coverage probability. This would result in a 90% probability that the half-width of the 90% confidence interval (CI) of the ratio of the geometric means for AUC and C_{max} is no larger than 20% in natural scale.

7.2 Parts B and C

The sample size is customary for Phase 1 studies evaluating safety and PK. The sample sizes are not based on statistical calculations. The sample sizes for each part of the study are considered sufficient to evaluate the primary objectives of this 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 subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. Changes from baseline in weight will also be listed, where baseline is defined as Day -1.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The 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:

Parts A & B – LY3298176 PK Parameters

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(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
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
CL	L/h	total body clearance of drug calculated after intravenous administration
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_Z	L	volume of distribution during the terminal phase after intravenous administration
V_{SS}/F	L	apparent volume of distribution at steady state following extra-vascular administration
V_{SS}	L	volume of distribution at steady state following intravenous administration
F	NA	absolute bioavailability (based upon geometric mean)

Part 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)
AUC(0-72)	ng.h/mL	area under the concentration versus time curve from time zero to 72 hours postdose
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

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.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this

parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on the last observed 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 quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

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

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile
A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

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

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

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

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

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

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values
Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

Part A

To assess the relative bioavailability of a single SC dose of LY3298176 administered as a solution formulation (test), compared to a lyophilized formulation (reference), AUC(0-∞), AUC(0-t_{last}) and C_{max} will be log-transformed and analyzed using a linear mixed effects model with treatment, period, and sequence as fixed effects and subject as a random effect. The difference in least squares means between the test formulation and reference formulation for each parameter will be exponentiated to yield ratios of geometric least squares means and their corresponding 90% CIs.

Example SAS code:

```
proc mixed data=DATA;
   class treatment period sequence subject;
   model log_pk = treatment period sequence / ddfm=kr;
   random subject;
   lsmeans treatment / pdiff cl alpha=0.1;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
run;
```

The t_{max} will be analyzed non-parametrically for the same comparison stated above. The Wilcoxon rank-sum test will be used to account for any possible period effect . The median of differences, approximate 90% CI, and p-values will be calculated.

Parts B and C

No formal statistical analysis will be performed. The PK parameters will be summarised by treatment, and listed.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the 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. AEs by day of onset will be presented for Part 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 AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 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.

9.4.2 Concomitant medication

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

9.4.3 Clinical laboratory parameters

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

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose (of each period in Part A), and 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 in frequency tables.

9.4.7 Injection-site pain assessment

Injection-site pain for subjects receiving SC injections/infusions will be assessed using the Visual Analog Scale (VAS). The data will be listed and summarized by treatment.

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. 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.

Clinically significant treatment-emergent ADAs will be flagged on the individual subject listings. Clinically significant treatment-emergent ADAs will be defined as any treatment-emergent ADAs at the last visit with:

- a high titer (≥1280) or an increasing titer from last measured value.
- an association with a moderate-to-severe injection site reaction or infusion-related reaction.
- cross-reactive and/or neutralizing binding of an ADA with endogenous glucagon-like peptide 1 (GLP-1) or glucose-dependent insulinotropic polypeptide (GIP).

To show the association of treatment-emergent ADAs with AEs, the frequency of treatment-emergent ADAs will be presented by MedDRA preferred term. Relationship between the presence of antibodies and the PK parameters of LY3074828 may be assessed graphically.

9.4.9 Blood glucose monitoring

Blood glucose data will be listed.

9.4.10 Hypoglycemic episodes

Episodes of hypoglycemia 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 events will be listed and summarized by treatment. The categories of hypoglycaemia are defined in the Protocol (Section 9.4.7.1).

9.4.11 Hepatic monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests will be performed to confirm the abnormality.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

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

9.4.12 Other assessments

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

9.4.13 Safety and tolerability statistical methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

10.1 Part B tolerability assessment

An interim analysis is planned after dosing 2 subjects in Part B of the study.

The possible outcomes following IV administration of a 0.5 mg dose of LY3298176 over 10 minutes are:

- LY3298176 tolerability is adequate; LY3298176 concentrations are measurable in the 2 subjects.
- LY3298176 tolerability is inadequate. To improve tolerability, the dose of LY3298176 may be reduced to 0.25 mg, administered over 10 minutes.
- LY3298176 tolerability is adequate; however, if LY3298176 concentrations cannot be adequately quantified, then a dose adjustment may be considered.

10.2 Interim database lock

An interim database lock will be performed after all subjects complete Part A, Period 2 up to Day 35. All available data in Part B will also be included. Database listings for the clinical laboratory, immunogenicity, and PK data will be created.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

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

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

13. DATA PRESENTATION

13.1 Derived Parameters

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

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

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

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