Protocol/Statistical Analysis Plan: I8B-MC-ITRR

Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro Following Single Dose Administration in Elderly and Younger Adults With Type 1 Diabetes Mellitus

NCT03166124

Approval Date:

STATISTICAL ANALYSIS PLAN

Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro Following Single Dose Administration in Elderly and Younger Adults with Type 1 Diabetes Mellitus

Statistical Analysis Plan Status: Final Version 2
Statistical Analysis Plan Date: 01-September-2017

Study Drug: LY900014

Sponsor Reference: I8B-MC-ITRR
CCI [redacted]

Clinical Phase I

Approval Date: 11-Sep-2017 GMT

1. TABLE OF CONTENTS

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(0-30min)	AUC from time zero to 30 minutes
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
CSII	Continuous subcutaneous insulin infusion
CRU	Clinical Research Unit
CV	Coefficient of variation
Early 50% t_{max}	Time to early half-maximal drug concentration
Early 50%TR_{max}	Time to half-maximal glucose infusion rate before TRmax
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
GD	glucodynamic
GIR	Glucose infusion rate
Gtot	Total amount of glucose infused
$Gtot_{(0\text{-}30min)}$	Total amount of glucose infused over 30 minutes
$Gtot_{(0\text{-}1h)}$	Total amount of glucose infused over 1 hour
ICH	International Council on Harmonisation
Late 50% t_{max}	Time to late half-maximal drug concentration
Late 50% TR_{max}	Time to half-maximal glucose infusion rate after TRmax
LS	Least square
LOESS	Locally weighted scatterplot smoothing
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable

NPH	Neutral protamine Hagedorn
PK	Pharmacokinetic
R_{max}	Maximum GIR
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SMPG	Self monitoring plasma glucose
SOP	Standard Operating Procedure
T1DM	Type 1 diabetes mellitus
TFLs	Tables, Figures, and Listings
T_{onset}	Time to onset of insulin action
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
TR_{max}	Time to R_{max}
VAS	Visual analogue scale
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 08 December 2016), amendment (a) (dated 09 March 2017), amendment (b) (dated 24 May 2017) and amendment (c) (dated 04 August 2017).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and glucodynamic (GD) 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 CCI [redacted]. 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 CCI [redacted] and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Council on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary

To evaluate the PK of insulin lispro following administration of a single 15-U subcutaneous (SC) dose of LY900014 compared to insulin lispro (Humalog) within each type 1 diabetes mellitus (T1DM) population (elderly and younger adults).

4.2 Secondary

To compare the GD during a euglycaemic clamp of LY900014 and insulin lispro (Humalog) following administration of a single 15-U SC dose in elderly and younger adults with T1DM.

To evaluate the safety and tolerability of the novel LY900014 formulation.

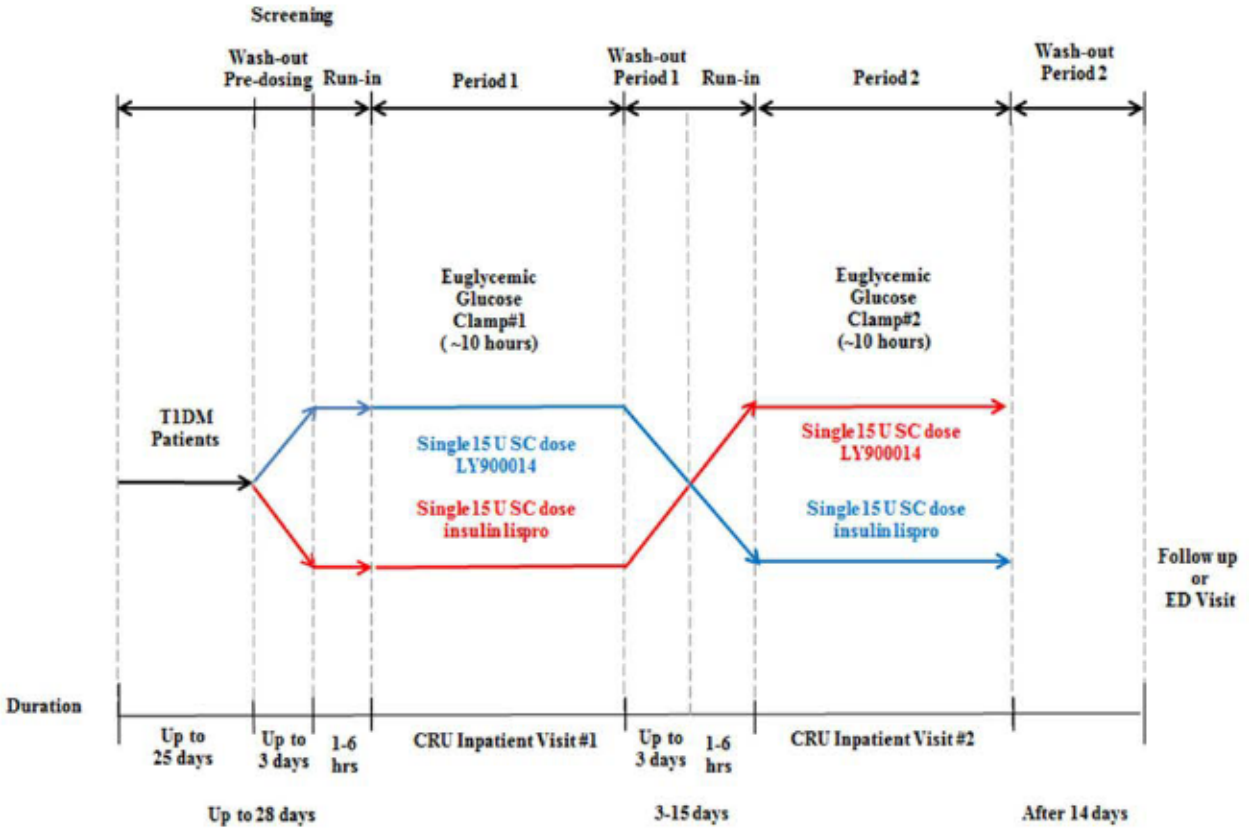
4.3 Exploratory

To evaluate whether the difference between LY900014 and insulin lispro in PK and PD parameters is similar between elderly and younger adults.

5. STUDY DESIGN

This is a Phase 1, randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study that compares the PK and GD of insulin lispro from LY900014 and insulin lispro (Humalog) following administration of a single 15-U SC dose in elderly and younger adults with T1DM who are either on multiple daily insulin injections or on continuous subcutaneous insulin infusion (CSII) via a sponsor-approved insulin pump. Study ITRR will be conducted at 1 or more sites.

Figure 1 illustrates the study design.



Abbreviations: CRU = clinical research unit; ED = early discontinuation; SC = subcutaneous; T1DM = type 1 diabetes mellitus

Figure 1. Illustration of study design

Patients will be randomized to 1 of 2 treatment sequences according to the actual randomization table provided to the site. Each patient will participate in a screening visit, 2 clinical research unit (CRU) inpatient dosing visits, and a follow-up visit. Before each dose, a run-in period of 1 to 6 hours to stabilize blood glucose will occur. Dosing visits will be separated by a wash-out period of 3 to 15 days, during which patients will resume their normal insulin treatment with the exemption of the insulin switch 48 to 72 hours prior to dosing as described in the protocol. At each visit, patients will receive either LY900014 or insulin lispro and undergo a euglycaemic clamp procedure where the time-concentration and time-action profiles of the study treatment will be evaluated simultaneously for up to 10 hours using an automated clamp device. Briefly, the aim of the euglycaemic clamp is to maintain euglycaemia after the administration of a dose of insulin by means of variable glucose infusion. The variable glucose infusion maintains or "clamps" glucose at a constant euglycaemic target; therefore, the glucose infusion rate (GIR) reflects the GD effect of the insulin.

All patients will be instructed to perform at least 4-point daily self-monitoring plasma glucose (SMPG), as well as continue their short-acting insulin during lead-in. The SMPG and prandial insulin doses should be recorded in the patient's diary, which will serve as a source document.

6. TREATMENTS

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

Study Treatment Name	**Treatment order in TFL**
LY900014	1
Humalog	2
Age Group Name	**Age Group order in TFL**
Elderly adults	1
Younger adults	2

7. SAMPLE SIZE JUSTIFICATION

Up to 42 younger adult and 42 elderly patients may be enrolled to ensure that at least 34 patients in each age group complete the study. Thirty-four completing patients in each age group will provide approximately 95% power to demonstrate a 40% increase in the insulin lispro area under the plasma concentration-time curve from time zero to 30 minutes (AUC[0-30min]) between LY900014 and Humalog within each age group. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The variability was estimated by analyzing a Lilly internal study that showed a log-scale standard deviation of within-patient difference in AUC(0-30min) of 0.5. Analysis of internal data showed a log-scale standard deviation of within patient difference in time to early half-maximal plasma concentration (early 50% t_{max}) of 0.5,

which provides approximately 95% power to show a 30% reduction in early 50% t_{max}, testing with an alpha level of 0.05 and a 2-sided CI.

In addition, the study is adequately powered to evaluate the GD parameters within each age group. There is approximately 80% power to detect a 20% decrease in both time to onset of insulin action (T_{onset}) and time to half-maximal GIR before TR_{max} (early 50% TR_{max}), and approximately 85% power to detect at least a 40% increase in total amount of glucose infused over 30 minutes (G_{tot}[0-30min]) and total amount of glucose infused over 1 hour (G_{tot}[0-1h]).

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all patients who received at least one dose of study drug.

The primary statistical analyses for PK will be conducted on those patients who receive at least 1 dose of study drug and have measurable insulin lispro concentrations.

The primary statistical analysis for GD will be conducted on those patients who complete at least 1 clamp procedure.

Supportive analyses will be done on the key PK and GD parameters for the patients who complete all treatment periods with evaluable data.

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.

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 [redacted] 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, hip and waist circumference, body weight, height and body mass index will be summarized by age group and listed. In addition, screening HbA1c, fasting blood glucose, fasting C-peptide, previous insulin therapy (basal and prandial) and duration of T1DM will be summarized and listed.

Alcohol consumption will be reported in the SDTMs in units of alcohol and will be converted to grams for the TFLs, where 1 unit is equal to 8 grams of pure alcohol.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Parameter Estimation

Patients who receive at least 1 dose of study drug and have measurable insulin lispro concentrations will be included in the PK analysis dataset.

PK analyses will be conducted using standard noncompartmental methods of analysis using CCI [redacted] on a computer that meets or exceeds the minimum system requirements for these programs. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management.

Free serum insulin lispro concentrations will be used to calculate several PK parameters, including early 50% t_{max}, time to late half-maximal plasma concentration (late 50% t_{max}), maximum observed concentration (C_{max}), t_{max}, $t_{1/2}$, and area under the plasma concentration-time curve from time zero to the last recorded time, AUC(0-30min), area under the plasma concentration-time curve from time zero to 1 hour, area under the plasma concentration-time curve from time zero to 10 hours, and area under the plasma concentration-time curve from time zero to infinity. Other parameters may be calculated as deemed appropriate. Additional partial area under the plasma concentration-time curves (AUCs) may be computed as necessary. The primary insulin lispro PK parameters for faster insulin lispro absorption analysis are early 50% t_{max} and AUC(0-30min).

Given the predicted low systemic concentrations of treprostinil, the PK analysis of treprostinil from the LY900014 dosing will be conducted using the available data. The primary analysis of the treprostinil concentrations will be focused on assessing time to maximum concentration (t_{max}) and C_{max}.

Although attempts will be made to adhere to the scheduled collection times (Section 2 of the protocol), it is recognized that situations arise that may compromise the scheduled times. Parameters will be individually calculated for each patient based on actual collection times and presented using summary statistics.

9.3.2 Pharmacokinetic Statistical Inference

Log-transformed C_{max}, AUC(0-30min) , AUC(0-1h), AUC(0-10h), AUC(2-10h), AUC(0-t_{last}), AUC(0-inf), CL/F and V_z/F for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog (reference), and their corresponding 95% CIs for each age group separately using the statistical model that includes treatment, sequence, and period as fixed effects and patient within sequence as a random effect.

Example SAS code:

```
proc mixed data=pk;
class patient period treatment sequence ;
model logpk = treatment period sequence / ddfm=kr;
random patient(sequence);
lsmeans treatment;
run;
```

The same model without log-transformation will be used for the analysis of the PK time parameters (early 50% t_{max}, late 50% t_{max}, t_{max}, and $t_{1/2}$). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's Theorem (Chow and Liu 2009[3]).

All analyses will be repeated for the population of patients who complete the study.

An exploratory analysis on the interaction between treatment and age group will be assessed using data from both age groups by a model similar to that for each age group, with the addition of age group and the interaction of treatment by age group as fixed effects. This test will be used to compare whether the LY900014 versus insulin lispro treatment effect is similar between the elderly and younger adult groups. The analysis will include all PK parameters analysed previously (both untransformed and log-transformed PK parameters).

Example SAS code:

```
proc mixed data=pk;
class patient period treatment sequence agegrp;
model logpk = treatment period sequence agegrp agegrp*treatment /
ddfm=kr;
random patient(sequence);
lsmeans agegrp*treatment;
run;
```

As treprostinil plasma concentrations after administration of LY900014 are expected to be very low, a descriptive statistical analysis may be conducted if sufficient data are available for this analysis.

9.4 Glucodynamic Assessment

9.4.1 Glucodynamic Parameter Estimation

GD assessments will be determined from the glucose clamp procedure, where the GIR over time will be used as a measure of insulin effect. GD analyses will be conducted on those patients who complete at least 1 clamp procedure. A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and age group using CCI

The fitted data for each patient will be used to calculate the following GD parameters: T_{onset}, maximum GIR (R_{max}), time to R_{max} (TR_{max}), early 50% TR_{max}, time to half-maximal GIR after TR_{max} (late 50% TR_{max}), total amount of glucose infused (G_{tot}), G_{tot}(0-30min), and G_{tot}(0-1h), Additional partial glucose AUCs, such as total amount of glucose infused over 2 hours, may be computed as necessary. The values of these GD parameters will be summarized by treatment group and age group through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated. The primary GD parameters for analysis are early 50% TR_{max}, G_{tot}(0-30min), G_{tot}(0-1h), and T_{onset}.

9.4.2 Glucodynamic Statistical Inference

The GD parameters will be listed and summarized by treatment and age group.

The statistical model will be the same as the model used for the analysis of the PK parameters. The non-time variables will be log-transformed prior to analysis and will include R_{max}, G_{tot}, G_{tot}(0-30min), G_{tot}(0-1h), and G_{tot}(0-10h). For GD parameters that have at least 1 patient with a value equal to zero, a value equal to the smallest non-zero observed GD value for that parameter divided by 2 will be added to all values, and the analysis of the log-transformed data will be performed.

The same model without log-transformation will be used for the analysis of the GD time parameters (T_{onset}, TR_{max}, early 50% TR_{max}, and late 50% TR_{max}). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's Theorem

All analyses will be repeated for the population of patients who complete the study.

An exploratory analysis on the interaction between treatment and age group will be assessed using data from both age groups by a model similar to that for each age group, with the addition of age group and the interaction of treatment by age group as fixed effects. This test will be used to compare whether the LY900014 versus insulin lispro treatment effect is similar between the elderly and younger adult groups. The analysis will include all GD parameters analysed previously (both untransformed and log-transformed GD parameters).

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 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 is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, age group, severity and relationship to the study drug. The frequency (the number of adverse events, the number of patients experiencing an adverse event and the percentage of patients experiencing an adverse event) of treatment-emergent adverse events will be summarized by treatment, age group, Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 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.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2016). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All clinical chemistry, hematology and urinalysis data will 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 and age group, together with changes from baseline, where baseline is defined as predose of Day 1.

Furthermore, values for individual patients will be listed.

9.5.5 Electrocardiogram (ECG)

ECG data will be listed for individual patients.

9.5.6 Blood Glucose Monitoring and Hypoglycemia

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 events (defined below) will be listed and summarized by treatment and age group.

Hypoglycemia is defined as follows:

•Documented Hypoglycemia:

- o Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by plasma glucose (PG) ≤70 mg/dL (≤3.9 mmol/L).
- o Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (≤3.9 mmol/L).

• **Unspecified hypoglycemia:** An event during which PG ≤70 mg/dL (≤3.9 mmol/L) but no information relative to symptoms of hypoglycemia was recorded

• **Probable symptomatic hypoglycemia:** An event during which symptoms indicative of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by PG ≤70 mg/dL [≤3.9 mmol/L]).

• **Severe hypoglycemia:** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

• **Nocturnal hypoglycemia:** Any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic or severe hypoglycemia) that occurs between bedtime and waking.

• **Overall hypoglycemia:** This optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category.

9.5.7 Injection Site Local Tolerability Assessment Data

Injection-site assessment data will be listed and summarized in frequency tables by treatment, age group and timepoint.

9.5.8 Pain measurements Using the Visual Analog Scale (VAS)

Intensity of pain data at the injection site as soon as practicably possible after the injection, and at multiple postdose timepoints, as reported by the patient and measured according to the 0- to 100-mm visual analog scale will be listed and summarized by treatment and age group.

The time 0 (immediately after dosing) data will be analyzed separately by age group ,using the Wilcoxon signed-rank test. The difference in medians between LY900014 and Humalog and the 95% CIs for the difference will be presented.

VAS data will also be summarized based on the following categories of score: 0, 1-10, 11-20, 21-30, 31-40, etc up to the maximum category by treatment, age group and timepoint and also the categories <=10 mm, <=20 mm and <=45 mm. The table will show number and percent of patients with observations in each category.

9.5.9 Immunogenicity

Immunogenicity data will be listed. The number of patients who have not-detected anti-insulin lispro antibody at pre-dose (for period 1) and detected anti-insulin lispro antibody at post-dose (measured in period 2 or follow-up) will be summarized by age group for combined treatments. The number of patients who have detected anti-insulin lispro antibody at pre-dose for period 1 and 57% increase from the pre-dose (for period 1) to post-dose (measured in period 2 or follow-up) will also be summarized in a similar way.

9.5.10 Other assessments

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

10. INTERIM ANALYSES

An interim analysis may be conducted after all patients in the younger adult group have completed the study to analyze the safety, PK and GD data in order to support regulatory submission. The Lilly clinical pharmacologist/Lilly study team is unblinded. The individuals and unblinded data are as specified in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

Data may be analyzed while the trial is ongoing, but no changes to the study design are planned. The results may help Lilly expedite final delivery and to enable planning of future studies. An assessment committee will not be formed.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

The protocol originally planned to analyse PK time parameters using a log-normal model. This was updated to a linear model with Fieller methodology added. Non-parametric analysis of the PK and GD data was originally planned in the protocol but this was removed for consistency with other studies. The VAS statistical analysis was updated to a non-parametric analysis due to issues observed in ITSC.

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.

3. Chow SC, Liu JP. Design and analysis of bioavailability and bioequivalence studies. 3 rd ed. Florida: Taylor and Francis Group, LLC; 2009:88-90.

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."

Leo Document ID = e5b3ab59-c94d-4bf1-9b50-fce862e61160

Approver: PPD
Approval Date & Time: 07-Sep-2017 18:38:14 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 11-Sep-2017 14:35:38 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 11-Sep-2017 15:08:51 GMT
Signature meaning: Approved