Statistical Analysis Plan Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro (Humalog) Following Single Dose Administration in Japanese Patients With Type 1 Diabetes Mellitus

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STATISTICAL ANALYSIS PLAN

Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro (Humalog) Following Single Dose Administration in Japanese Patients with Type 1 Diabetes Mellitus

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Study Drug: LY900014

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CCI [redacted]

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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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-30min)	Area under the concentration versus time curve from time zero to 30 minutes
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CRF	Case Report Form
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV%	Coefficient of variation
Early 50% t_{max}	Time to early half-maximal serum concentration
Early 50% TR_{max}	Early half-maximal GIR before time to maximum glucose infusion rate
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
GD	Glucodynamic
GIR	Glucose infusion rate
G_{tot}	Total amount of glucose infused
G_{tot}(0-30min)	Total amount of glucose infused over 30 minutes
G_{tot}(0-1h)	Total amount of glucose infused over 1 hour
G_{tot}(3h-END)	Total amount of glucose infused from 3 hours to the end of the clamp
G_{tot}(4h-END)	Total amount of glucose infused from 3 hours to the end of the clamp
ICH	International Council on Harmonisation
Late 50% t_{max}	Time to late half-maximal serum concentration
Late 50% TR_{max}	Time to half-maximal GIR after TRmax

LS	Least squares
LOESS	Locally weighted scatterplot smoothing
MDI	Multiple daily injections
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
NPH	Neutral protamine Hagedorn
PD	Pharmacodynamic
PG	Plasma glucose
PK	Pharmacokinetic
R_{max}	Maximum glucose infusion rate
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
T1DM	Type 1 diabetes mellitus
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
T_{onset}	Time to onset of insulin action
TR_{max}	Time to maximum glucose infusion rate
ULN	Upper limit of normal
VAS	Visual analog scale
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 07 November 2017) , the version 1 SAP (final version 1 dated 12 January 2018) and the version 2 SAP (final version 2 dated 27 April 2018).

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, PD 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 Objective

- To compare the PK of insulin lispro following administration of a single 15-U subcutaneous (SC) dose of LY900014 to insulin lispro (Humalog) in Japanese patients with type 1 diabetes mellitus (T1DM).

4.2 Secondary Objectives

- To compare the glucodynamics (GD) during a euglycemic clamp following administration of a single 15-U SC dose of LY900014 or insulin lispro (Humalog) in Japanese patients with T1DM.
- To evaluate the safety and tolerability of the proposed commercial formulation of LY900014.

5. STUDY DESIGN

This is a Phase 1, single center, randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study to evaluate the PK and GD of insulin lispro following a single 15-U SC administration of LY900014 compared to insulin lispro (Humalog) in Japanese patients with T1DM.

Patients will be randomized to 1 of 2 treatment sequences according to the actual randomization table provided to the site (Table 1). Each patient will participate in a screening visit (may occur up to 28 days prior to dosing), 2 inpatient dosing visits, and a follow-up visit (at least 14 days from last dose). Before each dose, a run-in period of approximately 1 to 6 hours to stabilize blood glucose will occur. Dosing visits will be separated by a washout period of 3 to 28 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 mentioned below. At each treatment period, patients will receive either LY900014 or insulin lispro (Humalog) and undergo a euglycemic 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 euglycemic clamp is to maintain euglycemia 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 euglycemic target; therefore, the glucose infusion rate (GIR) reflects the GD effect of the insulin. Figure 1 illustrates the study design.

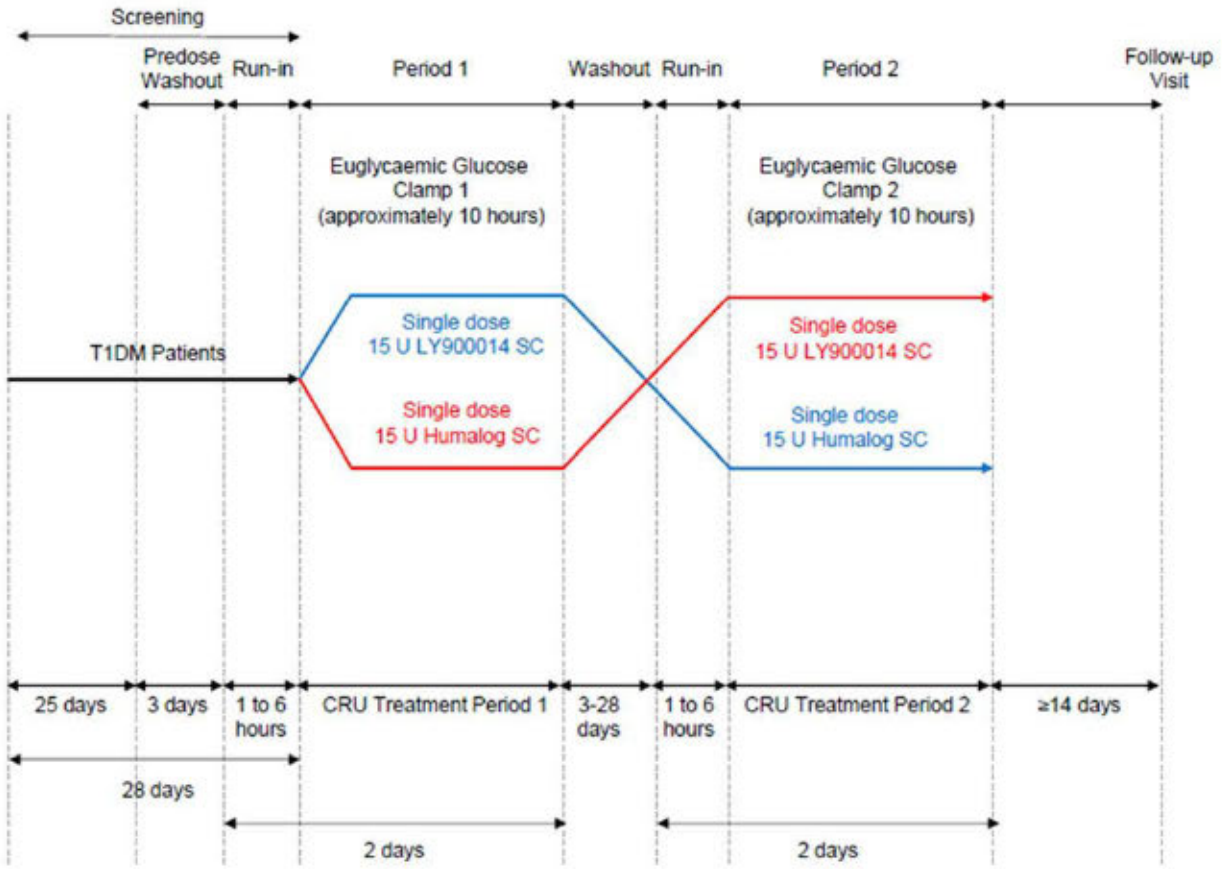
Prior to each dosing visit, patients with T1DM on multiple daily injections (MDI) have to discontinue their basal insulin, according to the following guidance:

- For patients using insulin degludec or insulin glargine U300, the last injection of insulin degludec or insulin glargine U300 should occur no later than 72 hours prior to dosing.
- For patients using insulin detemir or glargine, the last injection of insulin detemir or glargine should occur no later than 48 hours prior to dosing.
- For patients using neutral protamine Hagedorn (NPH) insulin or other intermediate-acting insulin, the last injection of NPH insulin or other intermediate-acting insulin should occur no later than 24 hours prior to dosing.

Patients requiring any infusion via continuous subcutaneous insulin infusion (CSII) of insulin lispro (Humalog) will switch to insulin glulisine (CCI) at least 8 hours prior to dosing. Basal infusion rate via CSII should occur no later than 3 hours prior to dosing. Any injection or bolus infusion via CSII of more than 6 U of short-acting insulin should not occur between 11 and 6 hours prior to dosing. Any bolus injection or bolus infusion via CSII should occur no later than 6 hours prior to dosing. Study governance considerations are described in detail in Appendix 3 of the protocol.

Table 1. Treatment sequences

Treatment Sequence	Treatment Period 1	Treatment Period 2
1	15 U LY900014 SC	15 U Humalog SC
2	15 U Humalog SC	15 U LY900014 SC



Abbreviations: CRU = clinical research unit; SC = subcutaneous; T1DM = type 1 diabete mellitus

Figure 1. Study design

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
15 U LY900014 SC	1
15 U Humalog SC	2

7. SAMPLE SIZE JUSTIFICATION

Up to 40 patients will be randomized in order that approximately 28 patients complete the study. Twenty-eight completing patients will provide approximately 92% power to demonstrate a 40% increase in the insulin lispro area under the concentration versus time curve (AUC) from time zero to 30 minutes (AUC[0-30min]) between LY900014 and Humalog. 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 (SD) of within-patient difference in AUC(0-30min) of 0.5. Analysis of internal data showed a log-scale SD of within-patient difference in time to early half-maximal serum 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. There is approximately 71% power to detect a 20% decrease in both time to onset of insulin action (T_{onset}) and time to early half-maximal GIR before time to maximum glucose infusion rate (TR_{max}) (early 50% TR_{max}), and approximately 81% 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]). In estimations, the log-scale SD of within-patient difference was used with 0.45 for T_{onset} and early 50% TR_{max}, and 0.6 for G_{tot}(0-30min) and G_{tot}(0-1h).

Patients who discontinue from the study prior to completion of both treatment periods with evaluable primary outcome data can be replaced to ensure that enough patients may complete the study. The replacement patient will adopt the original patient's randomized treatment sequence.

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 receive at least 1 dose of study drug and who complete at least 1 clamp procedure.

Supportive analyses will also be performed 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 SD, median, min, max and N; for log-normal data (e.g. the PK parameters: AUCs and maximum observed drug concentration [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 C C [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.

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 or treprostinil concentrations will be included in the PK analysis dataset.

The PK analyses will be conducted by Eli Lilly 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 serum concentration (late 50% t_{max}), C_{max}, time to maximum observed drug concentration (t_{max}), AUC from time zero to the last recorded time, AUC from time zero to 15 minutes, AUC(0-30min), AUC from time zero to 1 hour, AUC from time zero to 10 hours, and AUC from time zero to infinity. Other parameters may be calculated as deemed appropriate. Additional partial 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 of maximum observed drug concentration (t_{max}) and C_{max}.

Although attempts will be made to adhere to the scheduled collection times, 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} and AUC estimates for insulin lispro will be evaluated to estimate least squares (LS) geometric means, ratios of geometric means between LY900014 and Humalog, and their corresponding 95% CIs using the mixed-effects 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}, and t_{max},). LS means, treatment differences in LS 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.

Statistical significance will be achieved when the p-value for a test is less than 0.05.

The analyses described above will also be performed on the population of patients who completed and had evaluable PK data for both study periods.

9.4 Pharmacodynamic Assessment

9.4.1 Glucodynamic Parameter Estimation

Glucodynamic assessments will be calculated by Eli Lilly from the euglycemic clamp procedure, where the GIR over time will be used as a measure of insulin effect. Glucodynamic 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/or period using CCI software version 8.2. The fitted data for each patient will be used to calculate the following GD parameters: maximum GIR (R_{max}), TR_{max}, early 50% TR_{max}, time to half-maximal GIR after TR_{max} (late 50% TR_{max}), T_{onset}, G_{tot} over the duration of the clamp procedure, G_{tot}(0-1h), and G_{tot}(0-30min). The values of these GD parameters will be summarized by treatment 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}, Gtot(0-30min), G_{tot}(0-1h), and T_{onset}.

Additional partial glucose AUCs, such as Gtot over 2 hours (G_{tot}[0-2h]) and G_{tot} from 3 hours to the end of the clamp (G_{tot}[3h-END]), G_{tot} from 4 hours to the end of the clamp (G_{tot}[4h-END]), may be computed as necessary.

9.4.2 Glucodynamic Statistical Inference

The GD statistical model will be the same as the model used for the analysis of the PK parameters. The following variables will be log-transformed prior to analysis: R_{max}, G_{tot}, G_{tot}(0-30min), and G_{tot}(0-1h). Additional partial glucose AUCs, such as G_{tot}(0-2h) and G_{tot}(3-10h), may be analyzed as necessary. For GD parameters that have at least 1 patient with a value equal to zero, an analysis of original scale data (not log-transformed) will be performed as described below for the GD time parameters.

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 p-value for the difference between least-squares means will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The analyses described above will also be performed on the population of patients who complete and have evaluable GD data for both study periods.

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 the first dose. 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, severity and relationship to the study drug. The frequency (the number of AEs, the number of patients experiencing an AE and the percentage of patients experiencing an AE) of 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.

9.5.2 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.

Hypoglycemia is defined as follows:

- **Documented Glucose Alert Level (Level 1)**, Plasma Glucose (PG) ≤70 mg/dL (3.9 mmol/L):
    - **Symptomatic hypoglycemia**: an event during which typical symptoms of hypoglycemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
    - **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
- **Documented Clinically Significant Hypoglycemia (Level 2)** PG <54 mg/dL (3.0 mmol/L):
    - **Symptomatic hypoglycemia**: an event during which typical symptoms of hypoglycemia are accompanied by PG <54 mg/dL (3.0 mmol/L)
    - **Asymptomatic hypoglycemia**: an event not accompanied by typical symptoms of hypoglycemia but with PG <54 mg/dL (3.0 mmol/L)
    - **Unspecified hypoglycemia**: an event during which PG <54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded
- **Severe hypoglycemia (Level 3)**: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the patient has an altered mental status and cannot assist in their care, is

semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. PG measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L])

Other Hypoglycemia:

- **Nocturnal hypoglycemia**: any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycaemia) that occurs between bedtime and waking

- **Relative hypoglycemia**: an event during which typical symptoms of hypoglycemia, which do not require the assistance of another person, are accompanied by PG >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold

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

- **Probable symptomatic hypoglycemia**: An event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

9.5.3 Concomitant medication

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

9.5.4 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 patient data listings.

9.5.5 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. Furthermore, values for individual patients will be listed.

9.5.6 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. Where ECGs are measured in triplicate, the mean value will be used in all subsequent calculations. 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 of each period.

A serum insulin lispro concentration-QT analysis will be performed to assess the changes from baseline (Day 1 predose of each period) QTcF interval relative to serum insulin lispro concentrations following administration of LY900014 and Humalog. BLQ concentration data will be removed prior to analysis. The analysis will be performed by plotting change from baseline QTcF against serum insulin lispro concentrations, including all post dosing timepoints. The plot will be produced separately for each treatment.

A mixed effects analysis model will be performed on the change from baseline QTcF values and will include serum insulin lispro concentrations 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.

9.5.7 Hepatic Monitoring

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

The patients' 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 patient data listings.

9.5.8 Injection Site Local Tolerability Assessment

Injection site assessment data will be listed for individual patients and will be summarized in frequency tables by treatment and timepoint.

9.5.9 Visual Analog Scale (VAS) Assessment of Pain

The primary study assessment will be the intensity of pain at each injection site immediately after the injection (time 0) as reported by the patient and measured according to the 0- to

100-mm VAS. A Wilcoxon signed rank test will be used to analyze the time 0 (immediately after dosing) data. The difference in medians between LY900014 and Humalog and the 90% CIs for the difference will be presented. A descriptive summary will be provided for the following categories of scores: 0, 1-10, 11-20, 21-30, 31-40, etc. up to the maximum category by treatment for each time point.

9.5.10 Immunogenicity

The frequency of antibody formation to insulin lispro will be determined. The relationship between the presence (or absence) of antibodies and AEs will be assessed.

9.5.11 Other assessments

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

9.5.12 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

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

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

13. DATA PRESENTATION

13.1 Derived Parameters

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

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

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