Protocol/Statistical Analysis Plan: I8B-MC-ITRT

Effect of Injection Site on the Relative and Absolute Bioavailability of Single Dose of LY900014 in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

Effect of Injection Site on the Relative and Absolute Bioavailability of Single Dose of LY900014 in Healthy Subjects

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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(0-10h)	Area under the concentration versus time curve from time zero to 10 hours
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(0-∞)	Area under the concentration versus time curve from time zero to infinity
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL	Total body clearance of drug calculated after intravenous 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*)
G_{tot}	Total amount of glucose infused
GD	Glucodynamic
GIR	Glucose infusion rate
ICH	International Council on Harmonisation
IV	Intravenous
LOESS	Locally weighted scatterplot smoothing
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
R_{max}	Maximum glucose infusion rate

SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
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
tR_{max}	Time to R_{max}
V	Volume of distribution
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 24 May 2017 and amendment (a) dated 14 July 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 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 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 Objectives

- To determine the relative bioavailability of insulin lispro from LY900014 after SC injection into the thigh and deltoid compared to the abdomen in healthy subjects.
- To determine absolute bioavailability of insulin lispro following SC administrations of LY900014 into the thigh, deltoid, and abdomen compared to IV administration of LY900014 in healthy subjects.

4.2 Secondary Objectives

- To evaluate the tolerability of LY900014 in healthy subjects.
- To evaluate the GD during euglycemic clamp procedure of LY900014 after SC injection into the abdomen, thigh, and deltoid and IV in healthy subjects.

4.3 Exploratory Objectives

- To evaluate C-peptide levels after administration of LY900014.
- To determine plasma concentrations of the excipient, treprostinil, following administration of a single, IV 15-U dose of LY900014 in healthy subjects.

5. STUDY DESIGN

This is a Phase 1, single-center, open-label, 4-period, randomized, crossover, up to 10-hour euglycemic clamp study in approximately 28 healthy subjects to compare the insulin lispro PK and GD of LY900014 after SC administration of a 15-U dose at 3 different injection sites and a single IV bolus injection of 15 U. The SC injection sites are the abdomen, thigh, and deltoid.

Subjects will be required to attend the clinical research unit (CRU) on at least 6 occasions:

- screening visit (may occur up to 28 days before randomization)
- four treatment visits for the clamp procedure (study Periods 1 to 4) with a wash-out period of ≥3 days between discharge and the next admission to the CRU
- follow-up visit (at least 14 days after last dose), or early discontinuation.

Each subject will be randomly assigned to a treatment sequence and will be administered single doses of 15 U of LY900014 (on 4 occasions).

Subjects will be admitted to the CRU on the evening before each dosing day and will remain in the CRU for the duration of the clamp period and until discharge by the investigator. Subjects are expected to fast for at least 8 hours before each dose. Following dose administration, each subject will undergo a euglycemic clamp procedure of up to 10 hours. Upon completion of the clamp procedures, the subjects will be provided a meal and observed overnight. Subjects will be discharged from the CRU the next day after medical assessments.

Study governance considerations are described in detail in Appendix 3 of the protocol.

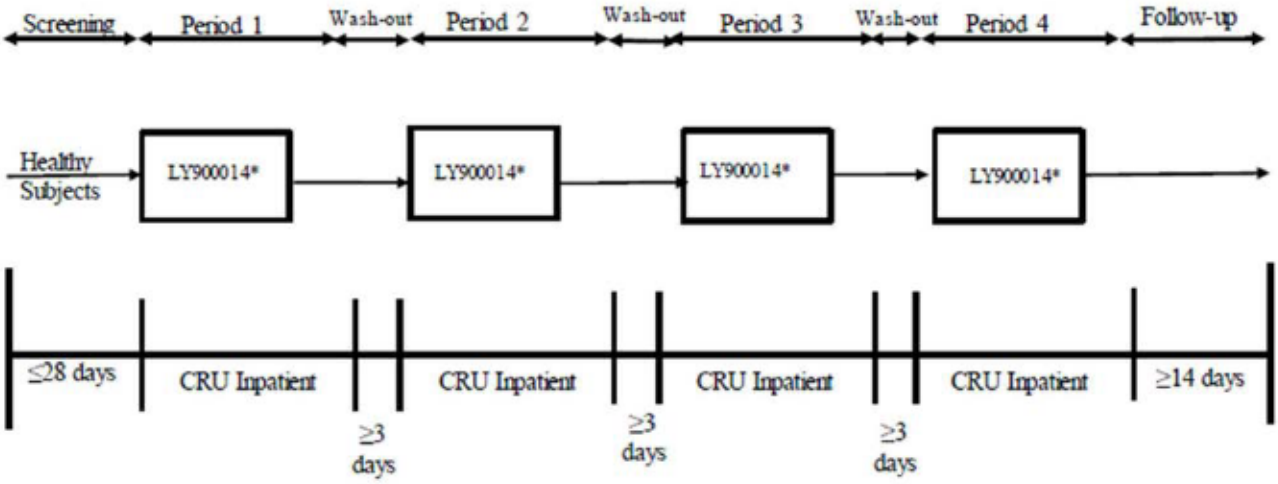

Figure ITRT.1 illustrates the study design.

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
1	LY900014 Abdomen	LY900014 Thigh	LY900014 Deltoid	LY900014 IV
2	LY900014 Deltoid	LY900014 Abdomen	LY900014 IV	LY900014 Thigh
3	LY900014 IV	LY900014 Deltoid	LY900014 Thigh	LY900014 Abdomen
4	LY900014 Thigh	LY900014 IV	LY900014 Abdomen	LY900014 Deltoid

Abbreviation: IV = intravenous.
Note: Subcutaneous injection sites are the abdomen, deltoid and thigh.

Figure ITRT.2 illustrates the treatment sequences.

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
15 U LY900014 Abdomen	1
15 U LY900014 Thigh	2
15 U LY900014 Deltoid	3
15 U LY900014 IV	4

7. SAMPLE SIZE JUSTIFICATION

Up to 28 subjects may be enrolled to ensure that at least 22 subjects complete the study. Twenty-two completing subjects will provide estimated 2-sided 90% confidence intervals (CIs) of the ratios of geometric means for AUC[0-∞] after SC injection into the thigh and deltoid, compared to the abdomen, to be within approximately 0.8 to 1.25 when the observed ratio is 1. This calculation is based on the assumption of a log-normal distribution and an estimate of intrasubject log-scale standard deviation of 0.2.

If subjects discontinue from the study before completion of all 4 study periods, replacement subjects may be enrolled up to 24 subjects following agreement between the investigator and the sponsor.

A replacement subject will be assigned the treatment sequence of the discontinued subject and complete that treatment sequence in its entirety.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Pharmacokinetic" population will consist of those subjects who receive at least 1 dose of study drug and have measurable insulin lispro concentrations and had evaluable PK data.

The "Glucodynamic" population will consist of those subjects who complete at least 1 clamp procedure.

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.

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 [redacted] or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, ethnicity, race, height, weight and body mass index (BMI) will be summarized and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Insulin lispro PK parameter estimates for LY900014 will be calculated using standard noncompartmental methods of analysis.

Free serum insulin lispro concentrations will be used to calculate several PK parameters, including maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), $t_{1/2}$, , and 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[0-t_{last}]), AUC from time zero to 10 hours (AUC[0-10h]), area under the concentration versus time curve from time zero to infinity (AUC[0-∞]), apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra-

vascular administration (Vz/F) will be determined. In addition, the total body clearance of drug calculated (CL), and volume of distribution (V) after IV administration also will be determined. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary.

Additional model-based analysis will be conducted as deemed appropriate to describe the elimination and absorption profiles.

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

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

The absolute bioavailability will be calculated using the ratio of the insulin lispro AUC(0-∞) following injection into the thigh, abdomen, and deltoid to the insulin lispro AUC(0-∞) following IV administration. A table of these percent absolute bioavailabilities will be presented.

9.3.2 Pharmacokinetic Statistical Methodology

Log-transformed AUC(0-∞) and C_{max} for insulin lispro will be evaluated to estimate geometric least-squares means (LSmeans), ratios of geometric LSmeans between injection sites (deltoid and thigh compared with the abdomen), and their corresponding 90% CIs using the statistical model that includes injection site, period, and sequence as fixed effects, and subject within sequence as a random effect. Data from the deltoid, thigh and abdomen injection sites will be included in the same model. The primary parameter for the statistical analysis of the relative bioavailability between injection sites will be the AUC(0-∞).

Example SAS Code:

```
proc mixed data=pk;
class subject site period sequence ;
model logpk = site period sequence / ddfm=kr;
lsmeans site / pdiff=control('abdomen') alpha=0.1;
random subject(sequence);
run;
```

The analyses will also be performed using all available data and repeated using the subset of the subjects who complete all treatment periods with evaluable data.

9.4 Glucodynamic Assessment

9.4.1 Glucodynamic Analysis

Glucodynamic assessments will be determined from the glucose clamp procedure, where the GIR over time will be used as a measure of insulin effect. Glucodynamic analyses will be conducted on those subjects 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 subject will be used to calculate the following GD parameters: maximum GIR (R_{max}), time to R_{max} (tR_{max}), and total amount of glucose infused (G_{tot})Additional GD parameters, may be computed as necessary. 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.

9.4.2 Glucodynamic Statistical Methodology

Log-transformed R_{max} and G_{tot} will be evaluated to estimate geometric LSmeans, ratios of geometric LSmeans between injection sites (deltoid and thigh compared with the abdomen), and their corresponding 90% CIs using the statistical model that includes injection site, period, and sequence as fixed effects, and subject within sequence as a random effect. Data from the deltoid, thigh and abdomen injection sites will be included in the same model. For GD parameters that have at least 1 subject 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. In addition, as a sensitivity analysis, a nonparametric analysis will be performed for that parameter based on the original parameters using a Wilcoxon Signed Rank test. Similar SAS code to that used to analyze the PK parameters will be used to analyze the GD parameters.

The analyses will also be performed using all available data and repeated using the subset of the subjects who complete all treatment periods with evaluable data.

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.

All AEs will be listed. Treatment-emergent AEs will be summarized by injection site, severity and relationship to the study drug. The frequency (the number of 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 19.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated.

9.5.2 Concomitant medication

Concomitant medication will be coded using the World Health Organisation (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 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 listed for individual subjects. Vital signs data will be summarized by treatment.

9.5.5 Electrocardiogram (ECG)

ECG data is not databased for this study so will not be reported.

9.5.6 Injection Site Assessment

Injection site assessment data will be listed for individual subjects and will be summarized in frequency tables by treatment. This is collected during the non-IV treatment periods.

9.5.7 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. Likewise, the relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may be assessed. The data will be listed and also presented in a frequency table.

9.5.8 Other assessments

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

9.5.9 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 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 AEs occurred for this study."

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