I8B-MC-ITRY Statistical Analysis Plan

A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Following Single Dose Administration in Health Chinese Subjects

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STATISTICAL ANALYSIS PLAN

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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]).

ADA	American diabetes association
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC(0-30 min)	Area under the concentration versus time curve from time zero to 30 minutes
AUC(0-1 h)	Area under the concentration versus time curve from time zero to 1 hour
AUC(0-10 h)	Area under the concentration versus time curve from time zero to 10 hours
AUC(3-10 h)	Area under the concentration versus time curve from time 3 hours 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
BQL	Below the quantifiable lower limit of the assay
C_{max}	Maximum observed drug concentration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
Early 50% t_{max}	Time to early half-maximal plasma concentration
Early 50% t_{Rmax}	Time to half-maximal GIR before t_{Rmax}
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}(0-1 h)	Total amount of glucose infused over 1 hour
G_{tot}(0-30 min)	Total amount of glucose infused over 30 minutes
G_{tot}(0-2 h)	Total amount of glucose infused over 2 hours
ICH	International Council on Harmonisation
Late 50% t_{max}	Time to late half-maximal drug concentration
Late 50% tR_{max}	Time to half-maximal GIR after tRmax
LS	Least square
LOESS	Locally weighted scatterplot smoothing
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
NA	Not applicable
PK	Pharmacokinetic
R_{max}	Maximum glucose infusion rate
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TBL	Total bilirubin
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
T_{onset}	Time to onset of insulin action
t_{Rmax}	Time to maximum glucose infusion rate
ULN	Upper limit of normal
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 draft created in September 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 . 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 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 evaluate the PK of insulin lispro following administration of single subcutaneous (SC) doses of 7 and 15 U of LY900014 and 15 U of Humalog in healthy Chinese subjects

4.2 Secondary Objectives

- To evaluate the GDs of insulin lispro during a euglycemic clamp procedure following SC doses of 7 and 15 U of LY900014 and 15 U of Humalog in healthy Chinese subjects
- To evaluate the safety and tolerability of the novel LY900014 formulation

4.3 Exploratory Objective

- Explore the formation of antibodies to insulin lispro.

5. STUDY DESIGN

This is a Phase 1, single center, randomized, subject-blind, 3-period, crossover study to evaluate the PK of insulin lispro for a novel LY900014 formulation in healthy Chinese subjects. Table 1 illustrates the study design.

After satisfying the study entry criteria, subjects will be randomized to 1 of 3 treatment sequences (Table 1). Subjects will be required to attend the clinical research unit (CRU) on 5 occasions:

- screening visit (up to 28 days prior to dosing [Day 1 of Period 1])
- 3 study periods, each comprising a 1 night inpatient stay from Day 1 to Day 1 for the clamp procedure (subjects may remain for longer in the CRU at the investigator's discretion for safety reasons)follow-up visit ≥14 days after the last dose, or early discontinuation

Subjects will be fasted (except for water and barley tea) for at least 8 hours prior to collection of clinical safety laboratory samples and dosing, and during glucose clamp procedures according to the Schedule of Activities (Section 2 of the protocol).

Each subject will participate in 3 inpatient visits; on Day 1 of each period, the time-concentration and time action profiles of insulin lispro will be evaluated simultaneously during a euglycemic glucose clamp of approximately 10 hours duration. 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. More information on the clamp methodology can be found in Section 9.6 of the protocol.

On completion of the euglycemic clamp, subjects will be provided with a meal and will undergo glucose monitoring to ensure that there is no risk of hypoglycemia. Serial blood samples will be collected during the 10-hour glucose clamp at the times specified in the Study Schedule (Section 2 of the protocol) to assess the PK parameters and GD parameters of LY900014. There will be a minimum of 3 days between study doses in consecutive periods.

A physician's medical assessment will be required before subjects are discharged from the CRU. There are no outpatient visits planned between study periods.

Safety assessments and an evaluation of local tolerability at injection sites will be performed as specified in the Study Schedule (Section 2 of the protocol). Local tolerability assessments will include injection-site assessments for signs of edema and erythema.

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

Table 1 Study Design

Treatment Sequence[a]	Period 1	Period 2	Period 3
1	15 U Humalog	7 U LY900014	15 U LY900014
2	7 U LY900014	15 U Humalog	15 U LY900014
3	7 U LY900014	15 U LY900014	15 U Humalog

Note: This is an example table; subjects will be assigned a treatment sequence according to the actual treatment schedule provided to the site.

[a] In each treatment period, 15 U Humalog or indicated doses of the LY900014 formulation will be administered.

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
7 U LY900014	1
15 U LY900014	2
15 U Humalog	3

7. SAMPLE SIZE JUSTIFICATION

Up to 15 subjects will be randomized in order that 12 subjects complete all periods of the study (4 per sequence).

Sample size is not based on a statistical power calculation. Sample size is considered suitable to characterize the PK profiles of insulin lispro, and to evaluate the safety and tolerability of single doses of LY900014 administered SC.

If the randomized subjects discontinue from the study prior to its completion, subjects can be replaced. The replacement subject will adopt the original subject's randomization schedule.

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 the investigational product and have evaluable PK data.

The "Glucodynamic" population will consist of all subjects who received at least one dose of investigational product and have evaluable GD 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 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 C C I 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.

9.3 Pharmacokinetic Analyses

9.3.1 Pharmacokinetic Parameter Estimation

Insulin lispro PK parameter estimates for LY900014 and Humalog will be conducted using standard noncompartmental methods of analysis using CCI 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 maximum observed concentration (C_{max}), time to maximum observed drug concentration (t_{max}), time to early half maximal plasma concentration (early 50% t_{max}), time to late half-maximal drug concentration (late 50% t_{max}), area under the concentration versus time curve (AUC) from time zero to 30 minutes [AUC(0-30min)], AUC from time zero to 1

hour[AUC(0-1h)], AUC from time zero to 10 hours [AUC(0-10h)], AUC from time 3 to 10 hours [AUC(3-10h)], AUC from time 0 to the last recorded time [AUC(0-t_{last}], AUC from time zero to infinity [AUC(0-∞)], half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$), 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. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary, such as AUC from time zero to 2 hours.

9.3.2 Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be summarized using standard descriptive statistics by Lilly.

9.4 Glucodynamic Analyses

9.4.1 Glucodynamic Parameter Estimation

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. The analyses will be performed according to the Lilly Global Pharmacokinetics, Pharmacodynamics, and Trial Simulation Divisional Standards.

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 The fitted data for each subject will be used to calculate the following GD parameters: maximum GIR (R_{max}), time to R_{max} (t_{Rmax}), time to half-maximal GIR before t_{Rmax} (early 50% t_{Rmax}), time to half-maximal GIR after t_{Rmax} (late 50% t_{Rmax}), T_{onset}, the total amount of glucose infused over the duration of the clamp procedure (G_{tot}), the total amount of glucose infused over 1 hour (G_{tot}[0-1h]), and the total amount of glucose infused over 30 minutes (G_{tot}[0-30min]). Additional partial glucose AUCs, such as G_{tot} infused over 2 hours (G_{tot}[0-2h]), may be computed as necessary. The values of these GD parameters will be summarized by treatment and/or period through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated.

9.4.2 Glucodynamic Statistical Inference

Glucodynamic parameters will be summarized using standard descriptive statistics by Lilly.

9.5 Safety and Tolerability Assessments

9.5.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is

defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

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 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.

9.5.2 Concomitant medication

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

Values for individual subjects will be listed.

9.5.5 Hepatic Monitoring

If a patient experiences elevated alanine aminotransferase (ALT) $\geq$3× upper limit of normal (ULN), alkaline phosphatase (ALP) $\geq$2× ULN, or elevated total bilirubin (TBL) $\geq$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.

9.5.6 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.

Hypoglycemia is defined as follows:

Documented Glucose Alert Level (Level 1), plasma glucose (PG) ≤70 mg/dL (3.9 mmol/L)

- **Documented symptomatic hypoglycemia:** with typical symptoms of hypoglycemia.
- **Documented asymptomatic hypoglycemia:** without typical symptoms of hypoglycemia.
- **Documented unspecified hypoglycemia**: with no information about symptoms of hypoglycemia available. (This has also been called unclassifiable hypoglycemia.)

Documented Clinically Significant Hypoglycemia (Level 2) with similar criterion as above except for threshold PG <54 mg/dL (3.0 mmol/L)

- **Level 2 Documented symptomatic hypoglycemia**
- **Level 2 Documented asymptomatic hypoglycemia**
- **Level 2 Documented unspecified hypoglycemia**

Severe hypoglycemia (Level 3)

- **Severe hypoglycemia:** Subjects had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG 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 documented hypoglycemic event (including severe hypoglycemia) that occurs at night and presumably during sleep. This is captured as hypoglycemia that occurs between bedtime and waking. This definition is more useful than the commonly used ~midnight to ~6 AM definition which does not take subjects' individual sleep times into consideration, and is consistent with the American Diabetes Association (ADA) recommendations of reporting events that occur during sleep (ADA 2005). It is also important to collect the actual time when

a hypoglycemic event occurred to allow further characterization of hypoglycemia timing (e.g., to allow analysis of frequency of events occurring across a 24-hr clock). Nocturnal hypoglycemia may occur at severity Levels 1, 2, or 3.

- **Relative hypoglycemia (also referred to as Pseudohypoglycemia [Seaquist et al. 2013]):** An event during which typical symptoms of hypoglycemia occur, that does not require the assistance of another person and is accompanied by PG >70 mg/dL (3.9 mmol/L). The PG value of subjects with chronically poor glycemic control can decrease so rapidly that subjects may report symptoms of hypoglycemia before their PG concentration falls below 70 mg/dL (3.9 mmol/L). Events with PG ≤70 mg/dL should not be categorized as relative hypoglycemia. Evaluation and statistical analysis of this category is optional. However, if a subject reports a relative hypoglycemia event where assistance from another person was received or the subject experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycemia event, and report it appropriately.

- **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia were present, but PG measurement was not reported.

- **Overall (or total) hypoglycemia:** This optional category combines most cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). It does not include relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in the category of overall (or total) hypoglycemia.

Only severe hypoglycaemic episodes will be reported separately as AEs. All episodes of severe hypoglycaemia will be reported as SAEs.

The goal of the euglycemic clamp is to maintain glucose concentrations at normal glycemic levels close to a predefined target. Therefore, glucose concentrations below 70 mg/dL will not routinely be recorded as hypoglycemic events during the glucose clamp procedure. However, at the discretion of the investigator, decrease in glucose concentrations may be recorded as a hypoglycemic event based on clinical concern or related to technical issues resulting in hypoglycemia. Glucose monitoring will continue after completion of the euglycemic clamp prior to discharge from the CRU at the discretion of the investigator.

9.5.7 Injection Site Assessment (Local Tolerability)

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

9.5.8 Immunogenicity

The frequency of antibody formation to insulin lispro will be determined.

9.5.9 Other assessments

Hip and waist circumference will be listed alongside body weight.

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

9.5.10 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

This is a subject-blind study; the investigator and Lilly study team is unblinded. Data may be analyzed while the trial is ongoing but no changes to the study design are planned. An assessment committee will not be formed. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

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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