Statistical Analysis Plan I8B-MC-ITSH

# A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 and Humalog across Different Subcutaneous Doses in Healthy Subjects

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Approval Date: 18-APR-2018

# STATISTICAL ANALYSIS PLAN

**A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 and Humalog across Different Subcutaneous Doses in Healthy Subjects**

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Study Drug: LY900014

Sponsor Reference: I8B-MC-ITSH
Covance CRU Study: CCI [redacted]

Clinical Phase I

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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 | Aminotransferase |
| AUC | Area under the concentration versus time curve |
| AUC(0-15min) | Area under the concentration versus time curve from time zero to 15 minutes |
| AUC(0-30min) | Area under the concentration versus time curve from time zero to 30 minutes |
| AUC(0-1h) | Area under the concentration versus time curve from time zero to 1 hour |
| AUC(0-10h) | Area under the concentration versus time curve from time zero to 10 hours |
| AUC(3-10h) | Area under the concentration versus time curve from time 3 hours to time 10 hours |
| AUC(0-∞) | Area under the concentration versus time curve from time zero to infinity |
| $C_{max}$ | Maximum observed drug concentration |
| CI | Confidence interval |
| 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 drug concentration |
| early 50% $tR_{max}$ | Time to half-maximal GIR before tRmax |
| 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 |

| | |
|---|---|
| Gtot(0-30min) | Total amount of glucose infused over 30 minutes |
| Gtot(0-1h) | 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 GIR after time of maximum glucose infusion rate |
| LOESS | Locally weighted scatterplot smoothing |
| LS | Least square |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRE | Magnetic resonance elastography |
| PK | Pharmacokinetic |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard deviation |
| 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 of maximum glucose infusion rate |
| ULN | Upper limit of normal |
| WHO | World Health Organization |

## 3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 26 June 2017) and version 1 of the SAP (dated 29 September 2017).

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

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

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Eli Lilly and Company and Covance EC Biometrics and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

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

## 4. STUDY OBJECTIVES

### 4.1 Primary Objective

- To evaluate the insulin lispro PK following subcutaneous (SC) doses of LY900014 compared to Humalog (at doses of 7, 15, and 30 U) in healthy subjects.

### 4.2 Secondary Objectives

- To evaluate the dose proportionality of the 3 dose levels of LY900014 as assessed by insulin lispro PK and GD measures.
- To evaluate the GD during euglycaemic clamp procedure following SC doses of 7, 15, and 30 U of LY900014 compared to Humalog in healthy subjects.
- To evaluate the tolerability of LY900014 in healthy subjects.

### 4.3 Exploratory Objectives

- Explore the formation of antibodies to insulin lispro.

- To assess C-peptide levels following administration of LY900014 and Humalog.

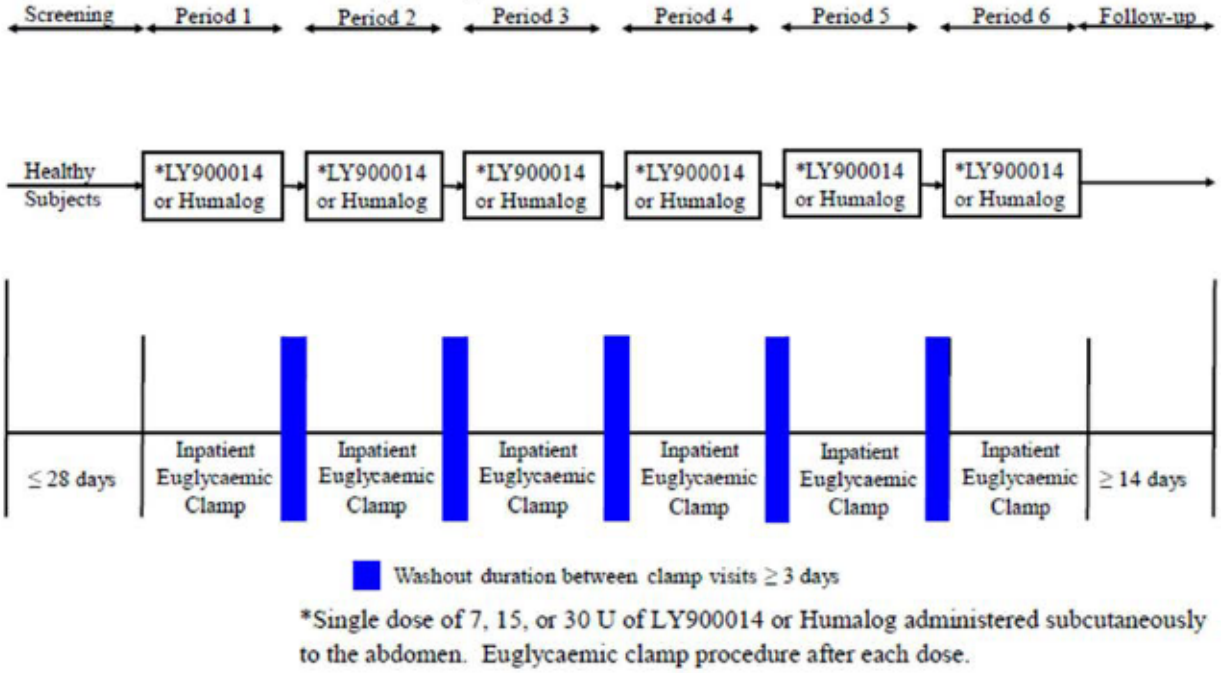
## 5. STUDY DESIGN

This is a Phase 1, randomised, subject- and investigator-blind, 6-period complete crossover study in up to 42 healthy subjects to evaluate the PK and GD characteristics across a range of LY900014 doses.

Approximately 34 subjects are expected to complete the study. Each subject will be randomised to 1 of 6 treatment sequences comprising single SC doses of 7, 15, and 30 U of LY900014 or Humalog administered SC in the abdominal wall (Table 1). A minimum of 3 days between study dosing of each consecutive study period will be required for an individual subject. Figure 1 illustrates the study design.

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

**Figure 1. Illustration of Study Design**




*Single dose of 7, 15, or 30 U of LY900014 or Humalog administered subcutaneously to the abdomen. Euglycaemic clamp procedure after each dose.

**Table 1. Treatment Sequence Example**

| Treatment Sequence | Period 1 | Period 2 | Period 3 | Period 4 | Period 5 | Period 6 |
|---|---|---|---|---|---|---|
| 1 | LY 7 U | LY 15 U | H 30 U | LY 30 U | H 15 U | H 7 U |
| 2 | LY 15 U | LY 30 U | LY 7 U | H 7 U | H 30 U | H 15 U |
| 3 | LY 30 U | H 7 U | LY 15 U | H 15 U | LY 7 U | H 30 U |
| 4 | H 7 U | H 15 U | LY 30 U | H 30 U | LY 15 U | LY 7 U |
| 5 | H 15 U | H 30 U | H 7 U | LY 7 U | LY 30 U | LY 15 U |
| 6 | H 30 U | LY 7 U | H 15 U | LY 15 U | H 7 U | LY 30 U |

Abbreviations: H = Humalog; LY = LY900014.
Note: this is only an example table for illustrative purpose; subjects will be assigned a treatment sequence according to the actual treatment randomisation schedule provided to the unblinded site pharmacist.

Subjects will be admitted to the clinical research unit (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 an euglycaemic clamp procedure of up to 10 hours. Upon completion of the clamp procedures, the subjects will be provided a meal and discharged from the CRU in the evening after medical assessments. Subjects may remain in the CRU if deemed necessary for safety monitoring, as determined by the investigator.

Subjects will be required to attend the CRU on at least 8 occasions:

- screening visit (up to 28 days prior to dosing)
- six treatment visits for the dosing and clamp procedure (study Periods 1 to 6) with a minimum period of at least 3 days between consecutive clamp visits
- follow-up visit (at least 14 days after the last dose), or early discontinuation

In the study, safety assessments and an evaluation of local tolerability at injection sites will be performed as specified in the Schedule of Activities (Section 2 of the protocol). Local tolerability assessments will include injection-site reactions within the following categories: pain on palpation, itching, erythema, oedema, and induration/infiltration.

## 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 SC | 1 |
| 15 U LY900014 SC | 2 |
| 30 U LY900014 SC | 3 |
| 7 U Humalog SC | 4 |
| 15 U Humalog SC | 5 |
| 30 U Humalog SC | 6 |

## 7. SAMPLE SIZE JUSTIFICATION

### 7.1 Sample Size Determination for Faster PK Absorption

Up to 42 subjects may be enrolled to ensure that at least 34 subjects complete the study.

Thirty-four completing subjects will provide approximately 96% 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 using prior internal studies that showed an average log-scale standard deviation (SD) of within-subject difference in AUC(0-30min) of CCI. Analysis of internal data showed a log-scale SD of within-subject difference in time to early half-maximal plasma concentration (early 50% time of maximum observed drug concentration [$t_{max}$]) of CCI. This sample size provides approximately 98% 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 80% power to detect a 20% decrease in both time to onset of insulin action ($T_{onset}$) and time to half-maximal glucose infusion rate (GIR) before time to $R_{max}$ ($tR_{max}$) (early 50% $tR_{max}$) and at least 85% power to detect at least a 40% increase in total amount of glucose infused ($G_{tot}$) over 30 minutes ($G_{tot}$[0-30min]) and $G_{tot}$ over 1 hour ($G_{tot}$[0-1h]).

### 7.2 Sample Size Determination for Dose Proportionality

Thirty-four completing subjects will provide greater than 95% power to demonstrate dose proportionality of AUC from time zero to 10 hours (AUC[0-10h]) and AUC from time zero to infinity (AUC[0-∞]). This is based on the assumption of a log-normal distribution and an estimate of intrasubject log-scale SD of CCI. There is also approximately 90% power to demonstrate dose proportionality of maximum observed drug concentration ($C_{max}$), assuming an intrasubject log-scale SD of CCI.

## 8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects who receive at least 1 dose of study drug.

The primary statistical analyses for PK will be conducted on those subjects 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 subjects who complete at least 1 clamp procedure.

Supportive analyses will be done on the key parameters for the subjects 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 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 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.

Data analysis will be performed using [redacted].

## 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 will be summarized and listed.

## 9.3 Pharmacokinetic Assessment

### 9.3.1 Pharmacokinetic Parameter Estimation

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 $C_{max}$, $t_{max}$, time to early half-maximal plasma concentration (early 50% $t_{max}$), time to late half-maximal drug concentration (late 50% $t_{max}$), AUC from time zero to 15 minutes [AUC(0-15min)], 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) and AUC(0-∞) will be determined. Additional partial AUCs may be computed as necessary, such as AUC from time zero to 2 hours.

The insulin lispro PK parameters for assessing faster insulin lispro absorption are the early 50% $t_{max}$ and AUC(0-30min).

The insulin lispro PK parameters for assessing reduction in the late insulin lispro exposure are the late 50% $t_{max}$ and AUC(3-10h).

The insulin lispro PK parameters for assessing dose proportionality are the $C_{max}$, AUC(0-10h), and AUC(0-∞).

Although attempts will be made to adhere to the scheduled collection times (Section 2 of the protocol), it is recognised 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.

### 9.3.2 Pharmacokinetic Statistical Inference

Log-transformed AUCs and $C_{max}$ for insulin lispro will be evaluated to estimate least-squares (LS) geometric means, ratios of LS geometric means between LY900014 and Humalog for each dose level, and their corresponding 95% CIs using the mixed-effects model that includes treatment, dose level, dose level-by-treatment interaction, and period as fixed effects and subject as a random effect.

Example CCI code:

```
proc mixed data=pk;
class subject period treatment dose ;
model logpk = treatment period dose dose*treatment / ddfm=kr;
random subject;
lsmeans dose*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 $t_{max}$). LSmeans, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences for each dose will be estimated from the model. 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 subjects who completed and had evaluable PK data for all study periods.

In addition, the degree of dose proportionality for insulin lispro will be assessed by fitting the power model (Smith et al. 2000[3]) to both AUC (AUC[0-10h] and AUC[0-∞]) and $C_{max}$ versus dose for each dose level of LY900014. The estimated ratio of dose-normalised geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. In addition, the slope and its 95% CI and the geometric LSmeans for each dose level tested will be produced. In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated. Log-transformed $C_{max}$ and AUC LSmeans, and 95% CI estimates for each dose will be back-transformed to provide the geometric means and the corresponding 95% CIs. The analyses will also be performed using the subset of the subjects who complete all treatment periods with evaluable data.

Example CCI code:

```
proc mixed data=pk1;
class subject;
model log_pk = log_dose / alpha=0.05 cl solution outpred=resids ddfm=kr;
random subject;
estimate 'xx mg' intercept 1 log_dose a / alpha=0.05 cl; /*Log value of xx*/
estimate 'yy mg' intercept 1 log_dose b / alpha=0.05 cl; /*Log value of yy*/
estimate 'zz mg' intercept 1 log dose c / alpha=0.05 cl; /*Log value of z*/
estimate 'zz mg - xx mg' log_dose d / alpha=0.05 cl; /*Difference in log
values of zz and xx*/
estimate 'zz mg - yy mg' log_dose e / alpha=0.05 cl; /*Difference in log
```

```
values of zz and yy*/
estimate 'yy mg - xx mg' log_dose f / alpha=0.05 cl; /*Difference in log
values of yy and xx*/
ods output solutionf=est;
ods output estimates=estims;
run;
```

## 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 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/or period using CCI The fitted data for each subject will be used to calculate the following GD parameters: $T_{onset}$, maximum GIR ($R_{max}$), time to $R_{max}$ ($tR_{max}$), time to half-maximal GIR before $tR_{max}$ (early 50% $tR_{max}$), time to half-maximal GIR after $tR_{max}$ (late 50% $tR_{max}$), total amount of glucose infused ($G_{tot}$), $G_{tot}$ over 30 minutes ($G_{tot}$[0-30min]), and $G_{tot}$ over 1 hour ($G_{tot}$[0-1h]). Additional partial glucose AUCs, such as $G_{tot}$ over 2 hours ($G_{tot}$[0-2h]), $G_{tot}$ from 3 hours to 10 hours ($G_{tot}$[3-10h]), from 4 hours to 10 hours ($G_{tot}$[4-10h]) may be computed as necessary. The values of these GD parameters will be summarised by treatment and/or period through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated. The primary GD parameters for earlier PD onset are early 50% $tR_{max}$, $G_{tot}$(0-30min), $G_{tot}$(0-1h), and $T_{onset}$.

### 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) along with any additional partial $G_{tot}$. 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% $tR_{max}$, late 50% $tR_{max}$). LSmeans, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences for each dose will be estimated from the model. 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 subjects who completed and had evaluable GD data for both study periods.

The degree of dose proportionality for the insulin lispro in LY900014 will be assessed by fitting the power model to $G_{tot}$ and $R_{max}$ versus dose for each dose level of LY900014.

The analyses will also be performed 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 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

Vital signs data will be listed for individual subjects.

### 9.5.5 Electrocardiogram (ECG)

The ECG data will be listed for individual subjects.

### 9.5.6 Hepatic Monitoring

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

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

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

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

### 9.5.7 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])

- **Severe hypoglycemia requiring medical attention**: a severe hypoglycemic event when patients require therapy by HCPs (EMTs, emergency room personnel, etc)

**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).

### 9.5.8 Injection Site Local Tolerability Assessment Data

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

### 9.5.9 Immunogenicity

The frequency of antibody formation to insulin lispro will be summarized by treatment and listed for individual subjects.

### 9.5.10 C-peptide

C-peptide data will be summarized by treatment. Figures of mean and individual C-peptide concentrations versus time will be presented by dose level for both treatments. In addition, individual plots overlaying the C-peptide concentration versus time with the insulin lispro serum concentration versus time will be presented.

Senstivity analysis removing subject(s) who could have potential confounding on the PD parameters will be performed as described in Section 9.4.2. Potential C-peptide confounding is

defined as when a substantial and implausible rise in C-peptide over baseline while the glucose infusion is ongoing.

### 9.5.11 Other assessments

Body weight, and hip and waist circumference will be listed.

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. Between the version 1 SAP and version 2 SAP, it was decided by Lilly to update the methodology for dealing with GD parameters with zero values. Additionally, some PK parameters were removed (CL/F, Vz/F and t½).

## 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. Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000;17(10):1278-1283.

## 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."

## 14. BLINDING AND UNBLINDING PLAN

Levels of unblinding are indicated in the table below. This table provides general guidance as to who will be allowed access to blinding information (including data or documents that can potentially unblind such as randomization codes, treatment assignments, and unblinded data) at various steps of the trial. For Interim Analysis (IA), appropriate IA team members, including the statistician, programmer and data manager will be identified and agreed upon between Lilly and any relevant Third Party Organizations (TPO).

Blinding information is kept strictly confidential and is accessible only by authorized personnel until unblinding of the trial as described below. All measures possible must be taken to maintain the blind; which means that access to the blinding information must be restricted to authorized personnel as described in the protocol and summarized in the table below.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. In such cases, the unblinding is to be conducted according to the protocol.

In the event of unplanned intentional unblinding, the detailed process, including information of the unblinded team, creating restricted access electronic folders, and measures taken to guard against inappropriate dissemination of treatment codes, will be described in a blinding plan revision or another appropriate document and review sought from the study team statistician.

| | **Study Timelines** | | | | |
|---|---|---|---|---|---|
| **Study Team Member** | **Screening** | **Randomisation** | **Treatment Phase** | **Follow-Up** | **Database Entry Lock** |
| **General** | | | | | |
| Clinical Supply Coordinator | NA | U | U | U | U |
| Randomization Statisticians | NA | U | U | U | U |
| ECG Reader | NA | NA | NA | NA | NA |
| Central Laboratory | NA | U | U | U | U |
| Local Laboratory | NA | NA | NA | NA | NA |
| Bio and Sample Analysis Lab | NA | U | U | U | U |
| **Clinical Site** | | | | | |
| Pharmacist | NA | U | U | U | U |
| Study/Dosing Nurse | NA | B | B | B | U |
| Technicians/Data entry staff | NA | B | B | B | U |
| Patient/Subject | NA | B | B | B | U |

| | Study Timelines | | | | |
|---|---|---|---|---|---|
| **Study Team Member** | **Screening** | **Randomisation** | **Treatment Phase** | **Follow-Up** | **Database Entry Lock** |
| Investigator(s) | NA | B | B | B | U |
| Study Monitor (Covance) | NA | U | U | U | U |
| **Covance Biometrics** | | | | | |
| Project Integration | NA | U | U | U | U |
| Data Management | NA | U | U | U | U |
| Programming | NA | U | U | U | U |
| Statistician | NA | U | U | U | U |
| Medical Writing | NA | U | U | U | U |
| PK Scientist/Associate | NA | U | U | U | U |
| **Lilly** | | | | | |
| CP/CRP/CRS/Biologist | NA | U | U | U | U |
| Consultant CPM | NA | U | U | U | U |
| CPA / Study Manager | NA | U | U | U | U |
| DSA | NA | U | U | U | U |
| SDTM Core Team | NA | U | U | U | U |
| Statistician | NA | U | U | U | U |
| Statistical Analyst | NA | U | U | U | U |
| Medical Writing | NA | U | U | U | U |
| PK Scientist/Associate | NA | U | U | U | U |
| PK Analyst | NA | U | U | U | U |
| PK Data Delivery | NA | U | U | U | U |
| CLO Representative | NA | U | U | U | U |

Abbreviations: B = blinded to study drug but not dose; CLO = clinical laboratory operations; CP = clinical pharmacologist; CPA = clinical pharmacology associate; CPM = clinical project manager; CRP = clinical research physician; CRS = clinical research scientist; DBL = database lock; DSA = data solutions associate; ECG = electrocardiogram; FPET = first patient enters treatment; LPET = last patient enters treatment; N/A = not applicable; PK = Pharmacokinetic; SDTM = study data tabulation model; TPO = third party organization; U = unblinded.