Statistical Analysis Plan: I8B-MC-ITRV(b)
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared

NCT03341299

Approval Date: 25May2018

STATISTICAL ANALYSIS PLAN

A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog® in Patients with T1DM

Statistical Analysis Plan Status: Final Version 3
Statistical Analysis Plan Date: 17 May 2018

Study Drug: LY900014

Sponsor Reference: I8B-MC-ITRV
Covance CRU Study: 1001215-8370486

Clinical Phase I

Approval Date: 25-May-2018 GMT

1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-15min)	Area under the concentration versus time curve from time zero to time 15 minutes
AUC(0-30min)	Area under the concentration versus time curve from time zero to time 30 minutes
AUC(0-1 h)	Area under the concentration versus time curve from time zero to time 1 hour
AUC(0-2 h)	Area under the concentration versus time curve from time zero to time 2 hours
AUC(0-7 h)	Area under the concentration versus time curve from time zero to time 7 hours
AUC(3-7 h)	Area under the concentration versus time curve from time 3 hours to time 7 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
EC	Early Clinical
ECG	Electrocardiogram
ED	Early discontinuation
e.g.	For example (Latin: *exempli gratia*)
GD	Glucodynamic

ICH	International Council on Harmonisation
Late 50% t_{max}	Time to late half-maximal drug concentration
LSmeans	Least square means
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
MMTT	Mixed meal tolerance test
PG	Plasma glucose
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SMPG	Self monitored plasma glucose
TBL	Total bilirubin
T1DM	Type 1 diabetes mellitus
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
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 10 August 2017), amendment (a) (dated 10 October 2017) and SAP version 1 (dated 09 November 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, GD 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 [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 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 PK of insulin lispro following a single subcutaneous (SC) injection of LY900014 and Humalog in patients with type 1 diabetes mellitus (T1DM).

4.2 Secondary Objectives

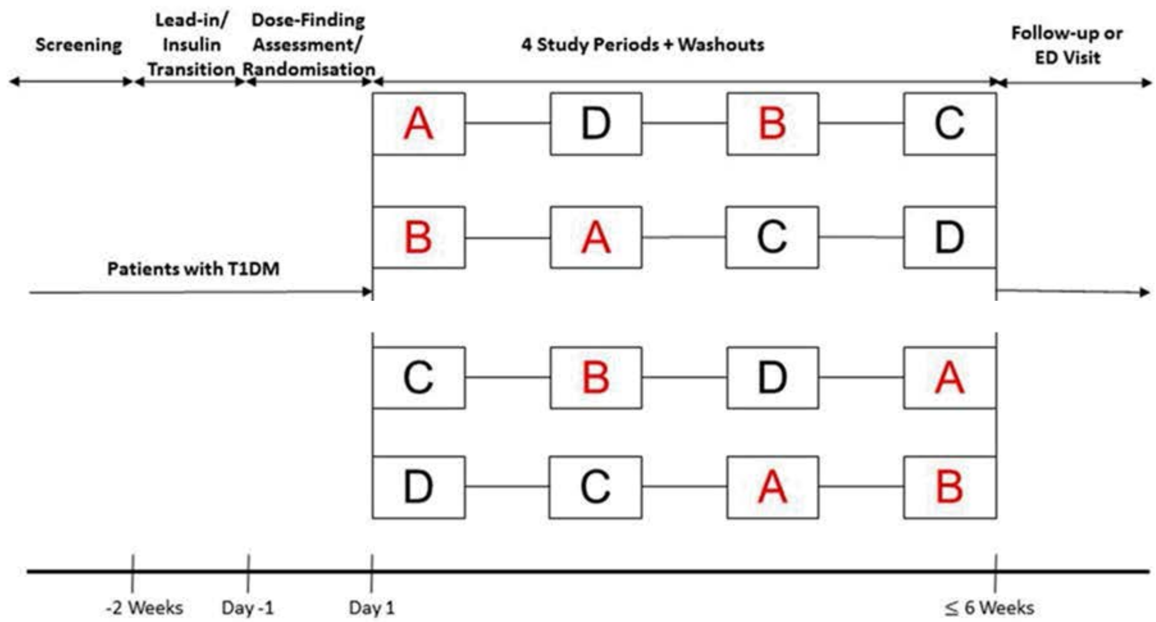
- To evaluate the effect of injection-to-meal timings (immediately before the start of meal, and 20 minutes following the start of the meal) on the GD response to LY900014 compared to Humalog, as measured by the mixed meal tolerance test (MMTT).
- To evaluate the tolerability of LY900014.

4.3 Exploratory Objective

- Explore the formation of anti-drug antibodies to insulin lispro.

5. STUDY DESIGN

This is a Phase 1, patient- and investigator-blind, randomized, 2-treatment, 4-period crossover study in patients with T1DM to evaluate the insulin lispro PK and GD characteristics of LY900014 compared to Humalog following single SC injections administered at 2 different injection-to-mealtime intervals; either immediately before or 20 minutes following the start of the test meal. This study may be conducted at 1 or more clinical research units (CRUs).



Treatment	LY900014 or Humalog	Dose Timing Relative to Meal (minute)*
A	LY900014	0
B	LY900014	+20
C	Humalog	0
D	Humalog	+20

* Time 0 is immediately before test meal

Abbreviations: ED = early discontinuation; T1DM = type 1 diabetes mellitus

Figure 1. Illustration of study design

Patients will be required to attend the CRU on at least 8 occasions (no more than 10 occasions if dose-finding and/or one MMTT rescheduled) as noted in the Study Schedule (see Section 2 of protocol):

- Informed consent
- Screening visit
- Lead-in and insulin transition period (see Section 9.2.1 of the protocol)
- 4 inpatient CRU study visits (including dose finding assessment [see Section 9.2.2 of the protocol])
- A follow-up visit

Eligible patients who have satisfied the entry criteria and completed all screening procedures will return to the CRU at least 2 weeks prior to Period 1 Day -2 to begin a lead-in and insulin transition period. When patients visit the CRU to begin the lead-in period, patients will receive instruction on general diabetes education including measurement of self-monitored plasma glucose (SMPG) and receive instruction on the insulin transition (see Section 9.2.1 of the protocol). During the insulin transition period, patients will transition from their current basal insulin therapy to site provided insulin glargine and Humalog [redacted] (see Section 9.2.1 of the protocol). Following insulin transition, patients will return to the CRU for the dose-finding assessment (see Section 9.2.2 of the protocol) on either the evening of Day -2, Period 1 or early morning of Day -1, Period 1. The dose-finding assessment will use Humalog administered immediately before a standardized liquid test meal to inform the dose of LY900014 and Humalog to be used during subsequent study MMTT assessments. Upon completion of the dose-finding assessment, patients will be randomised to 1 of 4 treatment sequences. Prior to the MMTT in each study period, patients will undergo a run-in period (see Section 9.2.3.1 of the protocol) to achieve a predetermined glucose target of 135 ±15 mg/dL (7.5 ±0.8 mmol/L). Once the glucose target has been attained, patients will proceed with the MMTT in which a single individualized SC dose of LY900014 or Humalog will be administered either immediately before the test meal or 20 minutes following the start of the test meal (see Section 9.2.3.2 of the protocol).

Doses of LY900014 and Humalog during the 4 study periods will be separated by a minimum washout of approximately 21 hours. The maximum duration allowed for all 4 periods is approximately 6 weeks. Patients will continue using site-provided Humalog and insulin glargine during the washout periods between MMTTs (see Section 7.7 for use of concomitant medication and basal insulin). During the washout periods, patients will be instructed to perform regular blood glucose monitoring (see Section 9.5.7 of the protocol).

Following completion of all study procedures in each Period, patients may be offered a meal and discharged from the CRU at the discretion of the principal investigator.

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

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
LY900014 (0 min)	1
LY900014 (+ 20 min)	2
Humalog (0 min)	3
Humalog (+ 20 min)	4

7. SAMPLE SIZE JUSTIFICATION

An initial 36 patients may be enrolled in order that approximately 30 patients complete the study. Thirty completing patients will provide greater than 95% power to demonstrate a 2-fold increase in the serum insulin lispro area under the concentration versus time curve from time zero to 30 minutes [AUC(0-30min)] between LY900014 and the Humalog. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The sample size will also provide greater than 95% power to demonstrate a 35% reduction of early 50% time to maximum observed drug concentration (early 50% t_{max}). The estimated standard deviation (SD) of within-subject difference on the log scale is 0.35 for AUC(0-30min) and 0.25 for early 50% t_{max}, according to an analysis of internal Lilly data (CCI [redacted]) for LY900014 and Humalog administered in a repeat-dose study.

With this sample size, there is approximately 80% power to detect a -30 mg·h/dL difference (LY900014 versus Humalog when both are given immediately before meals) in postprandial glucose ΔAUC[0-2h]. This is based on an analysis of ITRG which showed a SD of within-patient difference of 56.20 mg·h/dL on the original data scale.

Patients who are randomized but drop out before completing assigned treatment may be replaced to ensure that approximately 30 patients complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Safety” population will consist of all patients who received at least one dose of study drug, regardless of whether or not they completed all protocol requirements.

Primary statistical analyses of PK parameters will be conducted on the set of patients who have evaluable PK data from at least one period where LY900014 is dosed and at least one period where Humalog is dosed. The insulin lispro PK is not influenced by the injection-to-meal timing of dosing.

For the analyses of GD parameters, patients with evaluable GD data for both treatments (LY900014 and Humalog) within each injection-to-meal timing (immediately before the start of meal or 20 minutes after the start of the meal) will be included. If data for only one treatment (LY900014 or Humalog) exists for an injection-to-mealtiming, that data will not be included in the analysis.

Supportive analyses will be conducted on the set of patients who complete all treatment periods. A completer is defined as a patient with data for all 4 combinations of treatment and injection-to-meal timing.

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 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 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 sequential timepoints. The individual subject's change from baseline values will be used to calculate the mean change from baseline.

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, screening HbA1c, screening fasting blood glucose, screening fasting C-peptide, duration of T1DM, site ID, body weight, height, hip circumference, waist circumference and body mass index will be summarized and listed.

In addition, the following dosing data will be listed and summarized:

- Insulin dose at screening (stored in the concomitant dataset) for basal, bolus, and total.
- The average of days -3, -2 and -1 for Period 1 for basal insulin (glargine), bolus insulin (Humalog), and total daily insulin (Humalog and glargine).
- Dose finding dose for the MMTT (the dose administered for the dose finding and the dose selected after the dose finding on Day 1, Period 1 which will be used for all MMTT, and is the dose selected on the exposure dose finding page).

9.3 Pharmacokinetic Analyses

9.3.1 Pharmacokinetic Parameter Estimation

Patients who complete at least 1 MMTT and have measurable insulin lispro concentrations will be included in the analysis dataset for the PK analyses. PK analyses will be conducted using standard noncompartmental methods of analysis CCI [redacted]) on a computer that meets or exceeds the minimum system requirements for these programs. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

Free serum insulin lispro concentrations will be used to calculate several PK parameters, including time to early half-maximal drug concentration (early 50% t_{max}), time to late half-maximal drug concentration (late 50% t_{max}), maximum observed drug concentration (C_{max}), time to maximum observed drug concentration (t_{max}), AUC from time zero to time t, where t is the last time point with a measurable concentration [AUC(0-t_{last})], AUC from time 0 to 15 minutes [AUC(0-15min)], AUC from time 0 to 30 minutes [AUC(0-30min)], AUC from time zero to 1 hour [AUC(0-1h)], AUC from time zero to 7 hours [AUC(0-7h)], AUC from time 3 to 7 hours [AUC(3-7h)] and AUC from time zero to infinity [AUC(0-∞)]. 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.

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

The AUC(0-∞) will be the key PK parameter for the statistical analysis of the total insulin lispro exposure.

Although attempts will be made to adhere to the scheduled collection times, it is recognized that situations arise that may compromise sample collection at the scheduled times. Parameters will be individually calculated for each patient based on actual collection times and presented by summary statistics.

9.3.2 Pharmacokinetic Statistical Inference

Patients who did not keep identical insulin lispro doses for both treatments (LY900014 and Humalog) will be excluded from the statistical analysis of the PK parameters.

Log-transformed AUCs and C_{max} for insulin lispro will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog, and their corresponding 95% CIs of the ratios using the mixed-effects model that includes treatment (LY900014, Humalog) and period as fixed effects and patient as a random effect.

Example SAS code:

```
proc mixed data=pk;
class patient period treatment;
```

```
model logpk = treatment period / ddfm=kr alpha=0.05;
random patient;
lsmeans treatment;
run;
```

For AUC(0-∞), the analysis above will be used to produce an assessment of within-patient and between-patient variability for each treatment.

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},). Least-squares means (LSmeans), treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow and Liu 2009).

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

9.4 Glucodynamic Analyses

9.4.1 Glucodynamic Parameter Estimation

Patients who receive at least 1 dose of study drug and have evaluable GD data will be included in the analysis set for the GD analyses.

Data will be analyzed for the patients during each MMTT. The change from baseline values (the average of -30, -15, and 0 minutes represented as the 0-hour time point prior to the start of the MMTT) for each patient will be calculated. The area under the baseline subtracted glucose concentration versus time curve from time 0 to 2 hours (ΔAUC[0-2h] and area under the baseline subtracted glucose concentration versus time curve from time 0 to 5 hours post meal (ΔAUC[0-5h]) will be calculated. In addition, the change from baseline maximum glucose observed during the 5 hours postmeal and change from baseline 1 hour glucose and 2 hour glucose post the start of the meal will be calculated. Other partial ΔAUCs may be calculated, as deemed appropriate. Parameters will be individually calculated for each patient and presented by summary statistics. Glucose values post an intervention for either a hypoglycemic or hyperglycemic event during the MMTT will be excluded from the GD analysis.

9.4.2 Glucocodynamic Statistical Inference

Patients who did not complete the entire meal or had significant changes in nutrient consumption of the standardized liquid test meal or dose changes during the MMTTs across periods included in the statistical analysis will be excluded from all the statistical analyses of the GD parameters. Patients which don't have evaluable data for both treatments (Humalog and LY900014) for each injection-to-meal timing (immediately before the start of meal or 20 minutes after the start of the meal) will be excluded from the statistical analysis of the PD parameters.

Summary statistics (including number of patients, mean, SD or standard error, minimum, and maximum) will be presented by treatment and by timing of dose (all 4 combinations of treatment and timing of dose).

The GD parameters on the original scale (not log-transformed) will be analyzed using a statistical model that includes treatment, timing of dose (0 [immediately before the test meal], 20 minutes following the start of test meal), treatment-by-timing of dose interaction, and period as fixed effects and patient as a random effect. The p-value on the difference between LSmeans will be used to determine statistical significance and the corresponding 95% CIs for the LSmean ratios from Fieller's theorem will be presented.

Example SAS code:

```
proc mixed data=gd;
class patient period treatment timing;
model gd = treatment timing period treatment*timing / ddfm=kr
alpha=0.05;
random patient;
lsmeans treatment*timing;
run;
```

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

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 summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose for each period. Furthermore, values for individual subjects will be listed.

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. All hypoglycaemic events will be listed and summarized by treatment (LY900014 or Humalog) and dosing time. Each hypoglycaemic event will be ascribed in causality to the most recent meal-time insulin administration, including Humalog during lead-in, investigational product during MMTTs, Humalog between periods, or patient's own insulins taken during follow up.

The categories of Hypoglycemia are 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)

<u>Other Hypoglycemia:</u>

- **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

Immunogenicity data will be listed. The number of patients who have not-detected anti-insulin lispro antibody at pre-switch in the lead-in and detected anti-insulin lispro antibody at post-dose (measured in period 1, 3, or follow-up) will be summarized for combined treatments. The number of patients who have detected anti-insulin lispro antibody at pre-switch in the lead-in and 57% increase from the pre-switch to post-dose (measured in period 1, 3, or follow-up) will also be summarized in a similar way.

9.5.10 Other assessments

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

9.5.11 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 centre of the table, such as, “No serious adverse events occurred for this study.”