Statistical Analysis Plan (version 2): I8B-MC-ITSA

A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Compared to Humalog in Children, Adolescents, and Adults With Type 1 Diabetes Mellitus

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1. Statistical Analysis Plan: I8B-MC-ITSA: A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Compared to Humalog in Children, Adolescents, and Adults with Type 1 Diabetes Mellitus

LY900014

Study I8B-MC-ITSA is a randomised, patient- and investigator-blind, 2-part study, with each part containing a 2-period crossover assessment in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years) with type 1 diabetes mellitus to evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog given as a bolus either as a subcutaneous injection or via a continuous subcutaneous insulin infusion pump.

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Protocol I8B-MC-ITSA
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly:
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2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

3. Revision History

Statistical analysis Plan (SAP) Version 1 was approved prior to the first patient visit. This version is based on Protocol I8B-MC-ITSA approved on 12 October 2017 and amended on 21 December 2017. This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK), and glucodynamic (GD) data from this study.

This SAP is the second version approved prior to the completion of Part A of the I8B-MC-ITSA Study. The main changes are listed below:

- Clarifying that post-intervention blood glucose samples should not be included in any analysis to determine the PK/pharmacodynamic (PD) profile
- Adding that the observed values equal to 0 for PK parameters will be treated as missing.

4. Study Objectives

4.1. Primary Objective

The primary objectives of this study are as follows:

- Part A: To evaluate the PK of insulin lispro following a single subcutaneous (SC) bolus dose administered by injection of LY900014 compared to Humalog in children, adolescents, and adults with type 1 diabetes mellitus (T1DM)
- Part B: To evaluate the PK of insulin lispro following a single SC bolus dose administered by continuous subcutaneous insulin infusion (CSII) of LY900014 compared to Humalog in children, adolescents, and adults with T1DM

4.2. Secondary Objectives

The secondary objectives of this study are as follows:

- Part A: To evaluate the difference in GD response to LY900014 and Humalog administered by SC bolus injection as assessed using the liquid mixed meal tolerance test (MMTT), in children, adolescents, and adults with T1DM
- Part B: To evaluate the difference in GD response to LY900014 and Humalog administered by SC bolus via CSII as assessed using the liquid MMTT, in children, adolescents, and adults with T1DM
- Part A: To evaluate the tolerability of LY900014 following SC injection in children, adolescents, and adults with T1DM
- Part B: To evaluate the tolerability of LY900014 following SC bolus via CSII in children, adolescents, and adults with T1DM

5. Study Design

5.1. Summary of Study Design

This is a Phase 1, randomised, 2-part, patient- and investigator-blind, 2-period crossover study in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years) with T1DM currently using a CSII pump or multiple daily injection (MDI). The aim is to evaluate insulin lispro PK, GD, safety, and tolerability of LY900014 in comparison with Humalog (reference) following a single dose SC administration immediately prior to a standardised liquid meal.

This study is composed of 2 parts: Part A and Part B. During Part A, patients will receive a single dose of LY900014 and Humalog on 1 occasion each as SC bolus injection and in Part B a single dose of LY900014 and Humalog on 1 occasion each as SC bolus via CSII.

Patients will be randomised on Day 1 of Period 1 in Part A and Day -1 of Period 1 in Part B. For each age group, patients will be randomised to 1 of the 2 treatment sequences (first double-blind LY900014 then double-blind Humalog, and first double-blind Humalog then double-blind LY900014) in 1:1 ratio. In both parts, dosing in Period 1 and Period 2 can occur on consecutive days but not more than 22 days apart. For patients available for dosing on consecutive days, the medical assessments scheduled for Day -1 of Period 2 may be done on Day 1 of Period 1. Patients will undergo a rescreening visit if dosing visits between Part A and Part B are more than 28 days apart. Patients who participate in Part A may continue to Part B; however, patients who complete Part A but discontinue prior to Part B may be replaced by newly enrolled patients in Part B. Newly enrolled patients will be randomised to 1 of 2 treatment sequences after completing the screening and are expected to complete only Part B activities. Before each MMTT, a run-in period to stabilise blood glucose will occur.

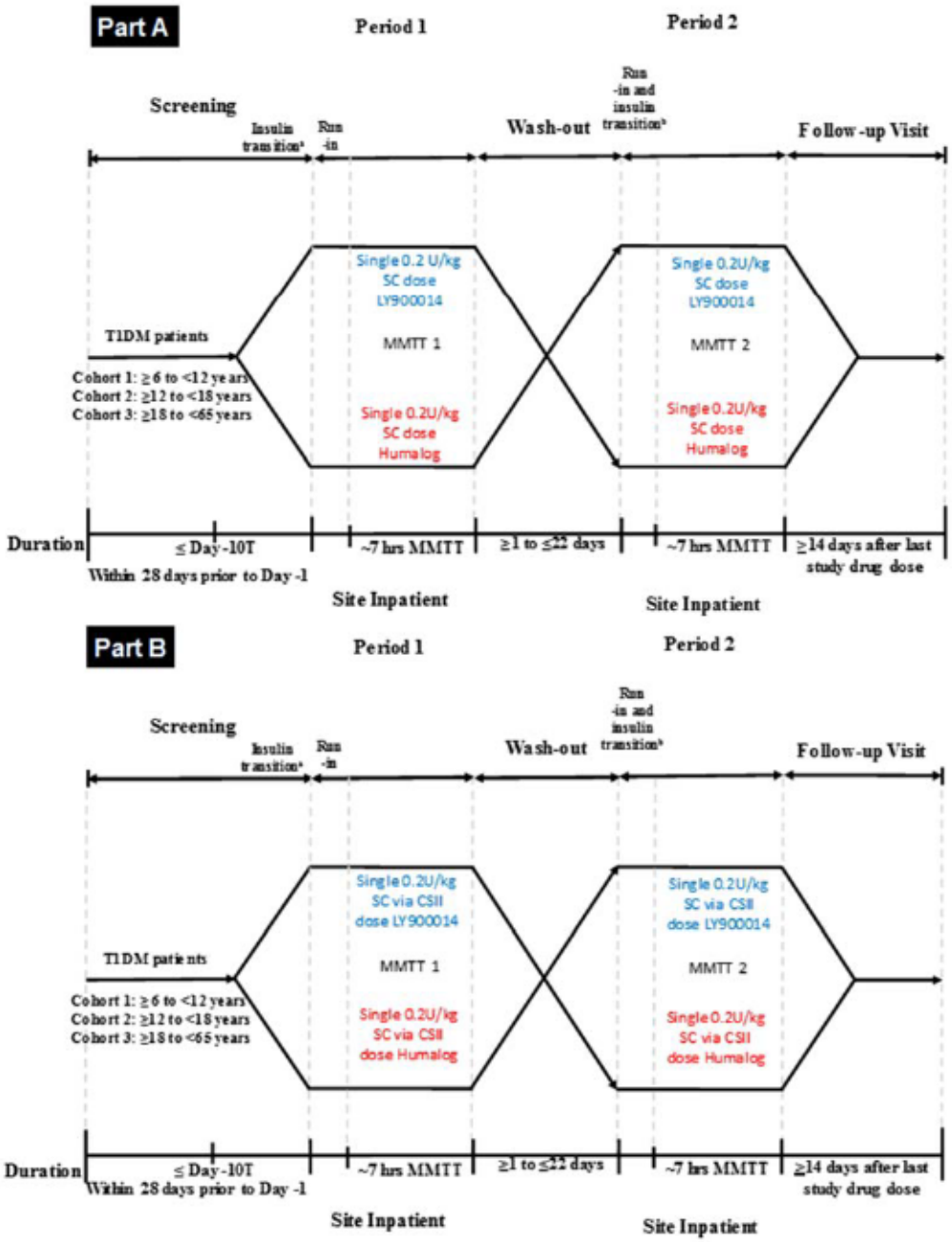
Figure ITSA.5.1 illustrates the design of Part A and Part B.

5.2. Determination of Sample Size

The number of patients needed to complete either Part A or Part B of this study was pre-set to 12 in each age group (6 to <12 years, 12 to <18 years, and 18 to <65 years). Twelve completing patients in each age group will provide approximately 90% power to demonstrate 60% increase in the insulin lispro area under the plasma concentration-time curve from time zero to 30 minutes ($AUC_{[0\text{-}30min]}$) between LY900014 and Humalog within each age group. The sample size will also provide greater than 85% power to demonstrate 30% reduction in time to early half-maximal drug concentration (early 50% t_{max}). The estimated standard deviation of within-subject difference on the log scale is 0.45 for $AUC_{(0\text{-}30min)}$ and 0.35 for early 50% t_{max}, according to an analysis of internal Lilly data and external published paediatric studies. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI).

Approximately 45 patients (approximately 15 patients in each age group) may be enrolled in the study to ensure approximately 36 patients complete both inpatient periods (i.e., 12 completers in each age group) for both parts of the study. If patients complete Part A but decline participation

in Part B or drop out from Part A, additional patients may be enrolled to ensure at least 36 patients complete Part B of the study.



Abbreviations: MDI = multiple daily injection; MMTT = mixed meal tolerance test; NPH = neutral protamine Hagedorn; SC = subcutaneous; T = telephone visit; T1DM = type 1 diabetes mellitus.

a Prior to Period 1, patients on MDI therapy with any basal insulin other than NPH twice daily will transition to NPH therapy twice daily approximately 7 to 3 days prior to Period 1.

b Insulin transition is applicable if Period 2 occurs >3 to 7 days after Period 1. The second MMTT assessment may occur on consecutive days but no more than 22 days after the first MMTT.

Figure ITSA.5.1. Illustration of study design.

6. A Priori Statistical Methods

6.1. General Considerations

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Data listings, summaries, and analyses will be performed by Covance Early Clinical (EC) Biometrics. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the clinical study report (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 Tables, Figures, and Listings (TFLs) may not be documented in the CSR.

The analyses for Part A and Part B of the study will be conducted separately using similar statistical methods. Treatment comparisons between LY900014 and Humalog will be conducted at an alpha level of 0.05 with a 2-sided CI within each age group for each part of study.

The age groups used in the PK and GD analyses will be determined by the age of the patient at initial screening. For patients who participated in both parts of the study, the age at screening of Part A will be used in the analyses for both parts. For patients newly enrolled for Part B only, the age at screening of Part B will be used.

The analysis populations are defined for each study part separately. Primary statistical analyses for PK parameters will be conducted on the set of patients who complete both treatment periods with an identical bolus insulin dose for the MMTTs and have measurable insulin lispro concentrations within each part of the study. Supportive analyses may be done on the key parameters for the patients who complete at least 1 treatment period and have measurable insulin lispro concentrations within each part of the study.

Primary statistical analyses for GD parameters will be conducted on the set of patients who complete both treatment periods with an identical bolus insulin dose for the MMTTs within each part of the study. Supportive analyses may be done on the key parameters for the patients who complete at least 1 treatment period for the MMTT within each part of the study.

The post-intervention glucose samples will be collected in the database; however, the post-intervention glucose data will be excluded from PK and GD analyses.

Safety analyses will be conducted for the set of patients receiving at least 1 dose of the study drug, whether or not they completed all protocol requirements.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients are assigned to analysis populations.

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented for continuous variables. Data from all 3 age groups will be pooled and analysed by a linear mixed-effect model for continuous variables unless otherwise stated in the succeeding subsections. The model will include treatment, sequence, period, age group, and the interaction of treatment and age group as fixed effects and patient

within sequence as a random effect. The primary comparison between LY900014 and Humalog for each age group will be based on the treatment difference or ratio of the given age group from the model.

For categorical data, frequency count and percentages will be presented in the summary table.

Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted, using all data that are databased. Summary statistics and statistical analyses will generally only be performed for patients included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

For weight and other clinical lab tests (based on data availability), mean change from baseline is the mean of all individual patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the time point. The individual patient's change from baseline values will be used to calculate the mean change from baseline using CCI

Additional exploratory analyses of the data will be conducted as deemed appropriate.

Data analysis will be performed using CCI or greater.

Table ITSA.6.1 is a list of the study treatment and age group names that will be used in the statistical TFLs.

Table ITSA.6.1 Treatment and Age Group Used in TFLs

Study Treatment Name	Treatment order in TFL
LY900014	1
Humalog	2
Age Group Name	**Age Group Order in TFL**
Children	1
Adolescents	2
Adults	3

Abbreviation: TFL = Table, Figure, and Listing.

6.2. Demographics and Patient Disposition

Patient disposition will be listed. The demographic variables age, sex, race, ethnicity, hip and waist circumference, body weight, height, and body mass index will be summarised by age group and listed. In addition, screening HbA1c, previous insulin therapy (basal and prandial), insulin administration method (CSII or MDI) at screening, and duration of T1DM will be summarised and listed.

Alcohol consumption will be reported in the SDTMs in units of alcohol and will be converted to grams for the TFLs, where 1 unit is equal to 8 grams of pure alcohol.

6.3. Pharmacokinetic Analysis

6.3.1. Pharmacokinetic Parameter Estimation

Patients who receive at least 1 dose of study drug and have measurable insulin lispro concentrations will be included in the PK analysis dataset. The post-intervention glucose data will not be included in the PK analyses.

Pharmacokinetic analyses will be conducted using standard noncompartmental methods of analysis CCI [redacted] and CCI [redacted] software CCI [redacted] on a computer that meets or exceeds the minimum system requirements for these programs. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilised if appropriate, warranted, and approved by global PK management.

Free serum insulin lispro concentrations will be used to calculate several PK parameters, including early 50% t_{max}, time to late half-maximal drug concentration (late 50% t_{max}), maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), half-life ($t_{1/2}$), and area under the plasma concentration time curve (AUC) from time zero to the last recorded time [$AUC_{(0\text{-tlast})}$], AUC from time zero to 30 minutes [$AUC_{(0\text{-30min})}$], AUC from time zero to 1 hour [$AUC_{(0\text{-1h})}$], AUC from time zero to 7 hours [$AUC_{(0\text{-7h})}$], and AUC from time zero to infinity [$AUC_{(0\text{-}\infty)}$]. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary.

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

Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

6.3.2. Pharmacokinetic Statistical Inference

The population for PK statistical analyses is defined in Section 6.1. The PK parameters will be summarised by treatment and age group for each part of the study.

Log-transformed C_{max} and AUC estimates for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog (reference), and their corresponding 95% CIs using the statistical model that includes treatment, sequence, period, age group, and treatment by age group interaction as fixed effects and patient within sequence as a random effect. Any observed values equal to 0 will be treated as missing for the analysis.

CCI [redacted]

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 treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow et al. 2009).

The PK analyses may be repeated for the population of patients who complete at least 1 treatment period and have measurable insulin lispro concentrations.

An exploratory analysis on the interaction between treatment and age group will be evaluated for all PK parameters using the same linear mixed-effect model for treatment comparison described previously. This test will be used to compare whether the LY900014 versus Humalog treatment effect is similar among all 3 age groups. The interaction effects will be evaluated using a significance level of 0.10.

6.4. Glucodynamic Analyses

6.4.1. Glucodynamic Parameter Estimation

Patients who receive at least 1 dose of study drug and have completed at least 1 MMTT procedure will be included in the analysis set for the GD analyses. The post-intervention glucose data will not be included in the GD analyses.

Data will be analysed 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 following the start of the MMTT) for each patient will be calculated. Mean change from baseline is the mean of all individual patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the time point. The area under the baseline subtracted glucose concentration versus time curve (ΔAUC) from time 0 to 2 hours postmeal ($\Delta AUC_{[0\text{-}2h]}$) and ΔAUC from time 0 to 5 hours postmeal ($\Delta AUC_{[0\text{-}5h]}$) 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 after 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 for each age group and treatment.

6.4.2. Glucodynamic Statistical Inference

The population for GD statistical analyses is defined in Section 6.1. The GD parameters will be summarized by treatment and age group for each part of the study.

The GD parameters on the original scale (not log transformed) will be analysed using the same model used for PK parameters. Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The above analyses may be repeated for the patients who complete at least 1 treatment period for the MMTT.

An exploratory analysis on the interaction between treatment and age group will be evaluated for all GD parameters using the same statistical model used for treatment comparison. This test will be used to compare whether the LY900014 versus Humalog treatment effect is similar among all 3 age groups. The interaction effects will be evaluated using a significance level of 0.10.

6.5. Safety and Tolerability Assessments

6.5.1. Adverse Events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the patient has provided written informed consent and is ongoing at consent. A nontreatment-emergent AE is defined as an AE that starts after informed consent but prior to dosing (prandial MMTT dosing for Part A and infusion set with study treatment inserted for Part B). A treatment-emergent AE is defined as an AE that occurs postdose or that is present prior to the first dose and becomes more severe postdose.

Treatment-emergent AEs will be summarized by treatment, age group, severity, and relationship to the study drug. The frequency (the number of AEs, the number of patients experiencing an AE, and the percentage of patients experiencing an AE) of treatment-emergent AEs will be summarized by treatment, age group, Medical Dictionary for Regulatory Activities 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.

All AEs will be listed. Any serious AEs will be tabulated.

6.5.2. Concomitant Medication

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

6.5.3. Clinical Laboratory Parameters

All clinical chemistry, haematology, and urinalysis data will be listed. Values for any clinical chemistry, haematology, and urinalysis values outside the reference ranges will be flagged on the individual patient data listings.

Additionally, clinical chemistry, haematology, and urinalysis data outside the reference ranges will be summarized by treatment sequence and age group.

6.5.4. Vital Signs

Vital signs data will be summarized by treatment and age group, together with changes from baseline, where baseline is defined as predose of Day 1. Furthermore, values for individual patients will be listed.

6.5.5. Blood Glucose Monitoring and Hypoglycemia

Hypoglycaemic events will be appropriately recorded in the CRF. In the case of a hypoglycaemic event, the actual blood glucose value, if measured, will be recorded in the CRF, together with any treatments administered. Each category of hypoglycaemic events (defined below) will be listed and summarized by treatment and age group for inpatient during the MMTT and inpatient run-in period (Part B only). "During the MMTT" refers to 0 to300 minutes post the start time of the meal or to the time of the first insulin dose after the MMTT, whichever occurs first. For the inpatient period prior to MMTT, the inpatient period after MMTT (from 300 minutes post the start time of the meal or the time of the first insulin dose after MMTT, whichever occurs first, to the end of inpatient visit), and the outpatient period (between Period 1 and Period 2 or between Period 2 and the follow-up visit), similar summary will be provided by age group independently of randomized treatment assignment. All hypoglycemia occurred during the study will be listed.

Hypoglycemia is defined as follows:

- **Documented Glucose Alert Level (Level 1), PG ≤70 mg/dL (3.9 mmol/L):**
  - **Documented symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
  - **Documented asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with PG ≤70 mg/dL (3.9 mmol/L)
  - **Documented unspecified hypoglycaemia:** an event during which PG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded
- **Documented Clinically Significant Hypoglycaemia (Level 2) PG <54 mg/dL (3.0 mmol/L):**
  - **Documented symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by PG <54 mg/dL (3.0 mmol/L)
  - **Documented asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with PG <54 mg/dL (3.0 mmol/L)

  - **Documented unspecified hypoglycaemia:** an event during which PG <54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded
- **Severe hypoglycaemia (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 his/her own care, is semiconscious or unconscious, or experienced coma with or without seizures. Plasma glucose 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 hypoglycaemia in children:** because children have limited ability to detect and/or self-treat hypoglycaemia, severe hypoglycaemia in children is an event in which children have altered mental status, and cannot assist in their care, are semiconscious or unconscious, or in coma with or without convulsions, and may require parenteral therapy (glucagon or IV glucose)
  - **Severe hypoglycaemia requiring medical attention**: a severe hypoglycaemic event when patients require therapy by health care providers (emergency medical teams, emergency room personnel, etc.)
- **Nocturnal hypoglycaemia:** any hypoglycaemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycaemia) that occurs at night and presumably during sleep
- **Relative hypoglycaemia:** an event during which typical symptoms of hypoglycaemia, 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) hypoglycaemia:** this optional category combines all cases of hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, the event is counted only once in this category
- **Probable symptomatic hypoglycaemia:** an event during which symptoms of hypoglycaemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

6.5.6. Injection-Site Assessment

Injection-site assessment data will be listed and summarized in frequency tables by treatment, age group, and time point.

6.5.7. Immunogenicity

Immunogenicity data will be listed and summarized for Parts A and B combined. The number of patients who have not detected anti-insulin lispro antibody at predose (for period 1 of Part A if patients participate both parts of the study or period 1 of Part B if patients participate Part B only) and detected anti-insulin lispro antibody at postdose (measured in all following visits after pre-dose) will be summarized by age group independently of randomized treatment assignment.

The number of patients who have detected anti-insulin lispro antibody at predose and 57% increase from the predose to postdose will also be summarized in a similar way.

6.5.8. Other Assessments

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

6.6. Interim Analyses

An interim analysis will be conducted after all patients complete Part A of this study to analyse the safety, PK, and GD data in order to support regulatory submission and future study design.

Data may be analysed while the trial is ongoing, but no changes to the study design are planned. Information that may unblind the study during the analyses will not be reported to study sites until the study has been unblinded. An assessment committee will not be formed.

7. Reference

Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd ed. Florida: Taylor and Francis Group, LLC; 2009:88-90.

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