Statistical Analysis Plan: I8B-MC-ITSZ (Version 1)

An Exploratory Study Assessing Time in Target Glucose Range Using a New Titration Scheme of LY900014 and Insulin Degludec in Participants with Type 1 Diabetes

NCT04585776

Approval Date: 05-Oct-2020

1. Statistical Analysis Plan: I8B-MC-ITSZ: An Exploratory Study Assessing Time in Target Glucose Range Using a New Titration Scheme of LY900014 and Insulin Degludec in Participants with Type 1 Diabetes

LY900014

Study I8B-MC-ITSZ (ITSZ) is a multicenter, single-group, open-label, Phase 2 study that will be conducted in participants with type 1 diabetes (T1D) currently treated with insulin degludec and a rapid-acting insulin analog in a multiple daily injection (MDI) regimen.

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Protocol I8B-MC-ITSZ
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 05-Oct-2020 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

Table of Contents

Appendix **Page**

3. Revision History

This statistical analysis plan (SAP) is the first version and is based on the protocol of I8B-MC-ITSZ approved on 08 June 2020 and the amendments (a) approved on 12 July 2020. SAP Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

4. Study Objectives

Table ITSZ.4.1 shows the objectives and endpoints of the study.

Table ITSZ.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the time that glucose values are within the target range 70 to 180 mg/dL from CGM use, after 35 days of using the study titration scheme with LY900014 treatment and degludec	Percentage of time with sensor glucose values between 70 and 180 mg/dL (both inclusive), with CGM use during the maintenance period
Secondary	
To evaluate ICR with LY900014 treatment	ICR at the end of the maintenance period
To evaluate the relationship between ICR and TDD with LY900014 treatment	ICR×TDD for the maintenance period
To evaluate total daily, basal, and prandial insulin dose with LY900014 treatment and degludec	Prandial: TDD ratio for the maintenance period
Tertiary/Exploratory	
To evaluate the safety of LY900014	Adverse events and vital signs
To explore the relationship between • ICR and TDD • ISF and TDD • ICR and ISF with LY900014 treatment	• Slope of the linear regression line of ICR or ISF on the reciprocal of TDD • Slope of the linear regression line of ICR on ISF, for the maintenance period
To explore ISF with LY900014 treatment	ISF at the end of the maintenance period
To explore glucose profiles, obtained from CGM use with LY900014 treatment	Actual and change from baseline in mean sensor glucose with CGM use during the maintenance period
To explore highest PPG level within 4 hours* after meal(s), obtained from CGM use, with LY900014 treatment	Actual and change from baseline in highest PPG level within 4 hours after meal(s), with CGM use during the maintenance period

Objectives	Endpoints
To explore the time from start of meal to highest PPG level within 4 hours* after meal(s), obtained from CGM use, with LY900014 treatment	Actual and change from baseline in minutes from start of meal to highest PPG level within 4 hours after meal(s), with CGM use during the maintenance period
To explore the percentage of time spent in hypoglycemic glucose ranges, obtained from CGM use, with LY900014 treatment	Actual and change from baseline in percentage of time with sensor glucose values <54 mg/dL, with CGM use during the maintenance period
To explore percentage of time spent in hyperglycemic glucose ranges, obtained from CGM use, with LY900014 treatment	Actual and change from baseline in percentage of time with sensor glucose values >250 mg/dL, with CGM use during the maintenance period
To explore within-day glucose variability, obtained from CGM use, with LY900014 treatment	Actual and change from baseline in within-day CV of sensor glucose, with CGM use during the maintenance period
To explore proportion of participants achieving CGM-based glycemic targets, with LY900014 treatment	The proportion of participants with percentage of time in • target glucose range, 70-180 mg/dL, >70% • hypoglycemia, <54 mg/dL, <1% • hyperglycemia, >250 mg/dL, <5%, with CGM use during the maintenance period
To explore fructosamine with LY900014 treatment	Fructosamine at the end of the maintenance period compared to baseline
To explore HbA1c with LY900014 treatment	HbA1c at the end of the maintenance period compared to baseline
To explore 1,5 Anhydroglucitol (AG) with LY900014 treatment	1,5 AG at the end of the maintenance period compared to baseline

Abbreviations: CGM = continuous glucose monitoring; CV = cardiovascular; HbA1c = hemoglobin A1c; ICR = insulin-to-carbohydrate ratio; ISF = insulin sensitivity factor; PPG = post-prandial glucose; TDD = Total Daily Dose.

*Excluding the glucose data from participants who have had the next meal event before the end of time interval.

5. Study Design

5.1. Summary of Study Design

Study I8B-MC-ITSZ (ITSZ) is a multicenter, single-group, open-label, Phase 2 study that will be conducted in participants with type 1 diabetes (T1D) currently treated with insulin degludec and a rapid-acting insulin analog in a multiple daily injection (MDI) regimen. The objective of the study is to assess the percentage of time glucose values are within the target range of 70 to 180 mg/dL after 35 days of titration using the study titration scheme of LY900014 and insulin degludec in participants with T1D.

The total duration of study participation for each participant is approximately 74 days across the following study periods:

- Screening, up to 10 days
- Lead in period, 11 days
- Treatment period
  - Titration period, 35 days
  - Maintenance period, 11 days
- Safety follow-up period, 7 days

Figure ITSZ.5.1 illustrates the study design.

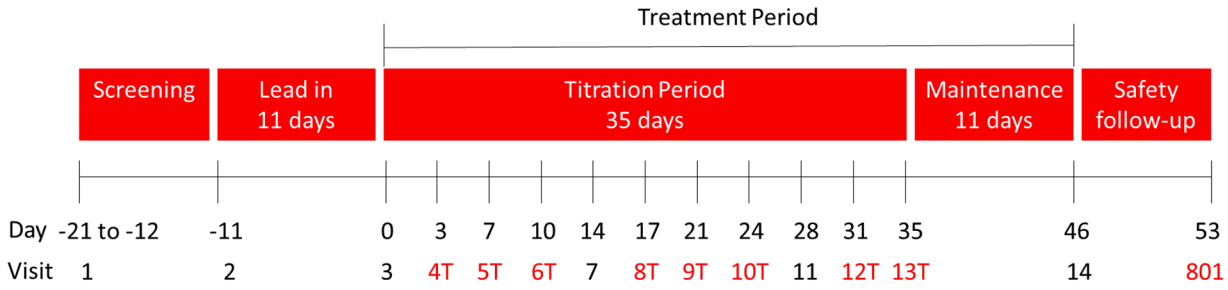

Figure ITSZ.5.1. Illustration of study design for Clinical Protocol I8B-MC-ITSZ.

5.2. Determination of Sample Size

Approximately 34 participants will be assigned to study treatment such that 30 evaluable participants will complete the maintenance period, assuming a 10% dropout rate.

The study is not strictly powered to demonstrate a statistically significant change from baseline in the primary endpoint (percentage of time with glucose within 70 to 180 mg/dL) because of the exploratory nature of the study.

Using a standard deviation of 12%, the sample will provide approximately 80% coverage probability that the half-width of the 95% confidence interval (CI) of the change from baseline in the primary endpoint falls within 4.93%.

5.3. Method of Treatment Assignment

The investigator should determine eligibility for treatment assignment before Visit 3. There will be no early enrollment if a participant meets the minimum 5-day requirement of 70% CGM readings per day before Visit 3.

For participants who are eligible for treatment assignment, Humalog will be discontinued, and LY900014 will be initiated using their current ICR, ISF, and DIA at Visit 3. All participants who are not currently administering insulin degludec in the morning should switch to morning administration with the investigator's guidance. All participants should continue administering degludec in the morning throughout the treatment period.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the clinical study report. Additional exploratory analyses of data will be conducted, as deemed appropriate.

The following populations are defined in Table ITSZ.6.1.

Table ITSZ.6.1. Patient Populations

Population	Description
Entered	All participants who give informed consent
Enrolled	All participants who continue the study after Visit 2
Treated	All assigned participants who receive at least 1 dose of the assigned study treatment after Visit 3

Unless otherwise specified, all efficacy and safety analyses will be conducted on the Treated Population. Unless otherwise noted, all tests will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. Comparison between baseline and endpoints will be performed at the full significance level of 0.05. No multiplicity adjustment will be made.

The definitions of baseline and post-baseline for the safety and efficacy analyses depend on which analysis period is being used. The following analysis periods will be used:

- Lead-in Period – from Day -11 to Day -1
- Treatment Period – from first dose to Day 46 (Visit 14) while on investigational product (IP) and from first dose to Day 46 (Visit 14) including all data regardless of IP use
- Treatment Period and Safety Follow-up Period – from first dose to Visit 801 including all data regardless of IP use

Table ITSZ.6.2 describes the rules for determining the patient population, baseline, and postbaseline observations for the different analysis periods.

The data on IP is defined based on the following rules:

- for data only measured at an office visit (eg, HbA1c and 1,5 Anhydroglucitol [1,5-AG]), if the office visit date (or laboratory sample collection date) is within 14 days of the date of last study drug dose of the current treatment period (treatment period), then postbaseline data measured at or prior to that office visit will be considered as data on IP for the current treatment period (treatment period).
- for data collected as running records with an exact date such as adverse events (AEs) where the date of the measures is not tied with the date of an office visit, postbaseline

data with date ≤ (last study drug dose date) will be considered as data on IP for the treatment period.

An analysis of covariance (ANCOVA) will be used to analyze continuous variables that are planned to be collected only for baseline and endpoint. The model will include baseline as a covariate.

A restricted maximum likelihood based, mixed model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables collected only at baseline and more than one scheduled post-baseline visits according to SoA in Section 1.3. All the longitudinal observations at each scheduled post-baseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint will include the fixed class effect of visit, and the random effect of patient. An unstructured covariance structure will be used to model the within patient errors. Significance tests will be based on least squares (LS) means and Type III tests. SAS PROC MIXED will be used to perform the analysis. If this analysis fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Compound symmetry with heterogeneous variances
- Toeplitz
- Autoregressive
- Compound symmetry without heterogeneous variances

The first covariance structure that converges will be used. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. If the analysis still does not converge with Compound symmetry without heterogeneous variances, only summary statistics will be provided.

For continuous measures, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum for both the actual and the change from baseline measurements. Least square (LS) means and standard errors derived from the analysis models will also be displayed for the actual and the change from baseline measurements.

For categorical measures, summary statistics will include sample size, frequency, and percentages. No statistical analyses will be conducted for baseline and endpoint comparison.

All CGM outcome variables will only be derived for Visit 3 (baseline) and Visit 14 (endpoint) based upon the CGM data collected from valid CGM days, excluding data (if any) that are collected while patients are temporarily off IP. A valid CGM day to be counted into the calculation for a visit must have at least 70% of the total measures that are supposed to be obtained.

For laboratory values, both conventional (CN) and Systeme International (SI) units will be presented. Therefore, both % and mmol/mol will be presented for HbA1c and both mg/dL and mmol/L will be presented for glucose measurements.

Table ITSZ.6.2. Baseline and Post-Baseline Definitions and Patient Population by Study Period and Type of Analysis

Baseline and Post-Baseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Post-Baseline Observations
Lead-In Period			
AEs	Enrolled Population	Prior to first dose of open-label Humalog (or Visit 2 date if the dose date is missing)	The entire lead-in period after first dose of open-label Humalog and prior to first dose of IP (or Visit 3 date if the dose date is missing)
Treatment Period (including Titration and Maintenance periods) and Safety Follow-Up Visit where applicable			
TEAEs	All patients in the Treated Population	Prior to first dose of IP (or Visit 3 if the dose date is missing)	From first dose of IP to last dose of IP AND From first dose of IP to Visit 801
Weight and vital signs	All patients in the Treated Population with a baseline and a post-baseline observation	Last of Visits 1 and 3	Visits 7, 11, 14 while on IP AND Visits 7, 11, 14 and 801 regardless of IP use
Basal, bolus, and total insulin doses, and bolus/total insulin dose ratios continuous analysis[a]	All Randomized Patients	Visits 3	Visit 14
ICR, ISF, and DIA	All patients in the Treated Population with a baseline and at least one post-baseline observation	Last value of Visits 2-3 prior to or on the date of the first dose of IP	Visit 4-14 while on IP
CGM outcome variables	All patients in the Treated Population with a baseline and a post-baseline observation	Based upon the CGM data collected for Visit 3 (baseline), excluding data (if any) that are collected while patients are temporarily off IP Humalog during the lead-in period	Based upon the CGM data collected for Visit 14 (endpoint), excluding data (if any) that are collected while patients are temporarily off IP during the maintenance period.
HbA1c	All Patients in the Treated Population with a baseline and a post-baseline observation	Visit 1	Visits 14 while on IP
Fructosamine	All Patients in the Treated Population with a baseline and a post-baseline observation	Visit 1	Visits 14 while on IP

1,5-AG	All Patients in the Treated Population with a baseline and a post-baseline observation	Visit 1	Visits 14 while on IP

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; CGM = continuous glucose monitoring; ICR = insulin-to-carbohydrate ratio; eCRFs = electronic case report forms; HbA1c = hemoglobin A1c; IP = investigational product; ISF = insulin sensitivity factor; DIA = Duration of Insulin Action; TEAE = treatment-emergent adverse event.

[a] The investigator will transcribe the LY900014 Humalog dose at Visit 3 (data from Day -10 to Day -1) and the LY900014 dose at Visit 14 (data from Day 36 to Day 45) to eCRF. These data will be used for summary and analyses of mean total daily basal dose, mean total daily bolus dose, mean total daily insulin dose, and the ratio of mean total daily bolus dose to mean total daily insulin dose.

6.2. Adjustments for Covariates

The MMRM model for the analysis of the primary efficacy endpoint will include the fixed class effect of visit, and the random effect of patient, as noted in Sections 6.9.

The ANCOVA model will include baseline as a covariate, as noted in Sections 6.9 to 6.10.

6.3. Handling of Dropouts or Missing Data

For CGM outcome variables only derived for Visit 3 (baseline) and Visit 14 (endpoint) based upon the CGM data, missing data will not be addressed. Only completers will be included in ANCOVA analysis.

For continuous variables collected at baseline and at Visit 14, missing data will not be addressed. Only completers will be included in ANCOVA analysis.

For continuous longitudinal variables collected at baseline and more than one scheduled post-baseline visits according to SoA in Section 1.3, missing data will be addressed by using a MMRM analysis. The MMRM model provides consistent estimator when data is missing at random. The model implicitly adjusts for missing data through a variance-covariance structure.

6.4. Multiple Comparisons/Multiplicity

Comparison between baseline and endpoints will be performed at the full significance level of 0.05. No multiplicity adjustment will be made.

6.5. Patient Disposition

Patient disposition will be displayed in a flowchart showing the number of patients entered, enrolled, treated, and discontinued across all study periods.

Frequency counts and percentages of the Treated Population completing and discontinuing from the study will be presented. Reasons for discontinuation from the study and study treatment will be summarized.

Frequency counts and percentages of all patients entered, enrolled, and discontinued from the study during the lead-in period will be summarized. Reasons for discontinuation during

screening will be summarized for the Entered Population. Reasons for discontinuation from the study during the lead-in period will be summarized for the Enrolled Population.

A listing of the primary reason for study/treatment discontinuation will be generated for the Enrolled Population.

A listing will be generated for the Treated Population, including the following variables but not limited to: investigator ID, patient ID, date of signature of informed consent form, first and last dose date of Humalog in the lead in period, study treatment assignment date, first and last dose date of LY900014 in the treatment period (titration and maintenance periods).

6.6. Patient Characteristics

A summary table will be generated for patient characteristics at study entry using the Treated Population. The following variables will be included but not limited to: age, age groups (<40 and ≥40 years, and <65, ≥65 years), sex, ethnicity, race, height, weight, body mass index (BMI), BMI groups (<25, ≥25 to <30, ≥30 to <35, and ≥35 kg/m^2). For continuous variables, the following statistics will be provided: mean, SD, minimum, maximum, and median. For categorical variables, summary statistics will include sample size, frequency, and percentage. A listing of patient characteristics at baseline will be provided.

A similar summary of diabetes characteristics will also be generated. The following variables will be included but not limited to: duration of diabetes, percentage of time with CGM values from 70 to 180 mg/dL over the lead in period, HbA1c at study entry.

For the Treated Population, the number and percentage of patients with historical conditions will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) (without regard to System Organ Class [SOC]), and the number and percentage of patients with preexisting conditions will also be summarized using MedDRA PT (without regard to SOC). Historical conditions are conditions that end prior to informed consent and preexisting conditions are conditions that are still ongoing at informed consent. Events will be ordered by decreasing frequency.

6.7. Treatment Compliance

No analysis for treatment compliance is planned for this study.

6.8. Concomitant Therapy

Concomitant medications will be summarized for the Treated Population for Titration and Maintenance periods combined. The percentages of patients receiving each concomitant medication will be summarized by treatment using PT nested within Anatomical Therapeutic Chemical (ATC) Level 3 code. Medications will be ordered by decreasing frequency within ATC level. Concomitant medication used during the lead-in period will also be summarized for the Enrolled Population.

6.9. Efficacy Analyses

6.9.1. Primary Outcome and Methodology

The primary objective of this study is to evaluate the percentage of time with glucose values within target range (70 to 180 mg/dL, both inclusive) after 35 days of using the study titration scheme with LY900014 treatment and degludec. Both actual and change from baseline will be derived and analyzed by the ANCOVA model as described in Section 6.1.

The primary analyses will be conducted on the Treated Population based upon the CGM data collected for Visit 3 (baseline) and Visit 14 (endpoint), excluding data (if any) that are collected while patients are temporarily off Humalog during the lead-in period or temporarily off IP during the maintenance period. Comparison between baseline and endpoints will be performed at the full significance level of 0.05.

Derivation and analysis of primary endpoint (derived for 24-hour, daytime and nighttime and by-meal) and other CGM endpoints are described in Section 6.13.

6.9.2. Other Secondary Efficacy Analyses

The analyses described in Section 6.9.2 will include data collected from the Treated Population. Details for the CGM analyses are described in Section 6.13. Continuous secondary efficacy variables, as well as the change from baseline for these variables, will be analyzed by the MMRM or ANCOVA model as described in Section 6.1.

The ICR data from the day before a scheduled visit will be transcribed in eCRF at Visit 2, Visit 3 through Visit 14 and ET Visit, respectively. Any changes and associated to meals for ICR during the Treatment period will be captured. A listing will be provided to include ICR data collected at Visit 2, changes in ICR by meal captured during Treatment period in the eCRF. An MMRM model similar to that for the primary endpoint will be used to analyze actual and change from baseline in ICR.

For the following secondary efficacy endpoints data collected for Visit 3 (baseline) and Visit 14 (endpoint), an ANCOVA model as described in Section 6.1 will be used:

- actual and change from baseline in insulin doses, including mean total daily basal (U/day, U/kg/day), mean total daily bolus (U/day, U/kg/day), and mean total daily insulin dose (U/day, U/kg/day) and mean total daily bolus / total daily insulin dose ratios (%)

The investigator will transcribe the Humalog dose at Visit 3 (data from Day -10 to Day -1) and LY900014 dose at Visit 14 (data from Day 36 to Day 45) to eCRF. To assess the insulin doses over the course of 10 days for each visit, the mean total daily basal dose will be derived based on CGM data collected during lead in period (data from Day -10 to Day -1) and maintenance period (data from Day 36 to Day 45), and mean total bolus doses will be derived based upon the eCRF data collected at Visit 3 and Visit 14.

Relationships between ICR and TDD will be evaluated through regression lines (ICR versus 1/TDD) and compared with the “500 Rule,” which is currently used in clinical practice where

ICR = 500/TDD (Section 2.1 in study protocol) by visit. Regression lines with and without intercept will be analyzed. The analyses will be conducted based upon ICR and mean total daily insulin dose (U/day) collected for Visit 3 and Visit 14, separately.

6.9.3. Exploratory Efficacy Analyses

Continuous exploratory efficacy variables, as well as the change from baseline for these variables, will be analyzed by the MMRM or ANCOVA model as described in Section 6.1, unless otherwise specified.

The following analyses will be conducted based upon ISF (mg/dL per insulin unit), mean total daily basal dose (U/day), mean total daily insulin dose (U/day), and weight (kg) collected for Visit 3 and Visit 14, separately. Relationships between the following endpoints will be explored through regression lines (King et al. 2007a, 2007b) by visit, separately. Regression lines with and without intercept will be analyzed.

- ISF and 1/TDD
- TBD and weight

The ICR (grams per insulin unit) and ISF (mg/dL per insulin unit) data from the day before a scheduled visit will be transcribed in eCRF at Visit 2, Visit 3 through Visit 14 and ET Visit, respectively. Relationships between ICR and ISF will be explored through regression lines with and without intercept by scheduled visit, separately.

The ISF and DIA data from the day before a scheduled visit will be transcribed in eCRF at Visit 2, Visit 3 through Visit 14 and ET Visit, respectively. Any changes for ISF and DIA during the Treatment period will be captured. A listing will be provided to include ISF and DIA data collected at Visit 2, changes in ISF and DIA by meal captured during treatment period in the eCRF. An MMRM model similar to that for the primary endpoint will be used to analyze actual and change from baseline in ISF and DIA, respectively.

Actual and change from baseline in fructosamine, HbA1c and 1,5-AG will be summarized and analyzed by ANCOVA.

In addition, CGM outcomes that are not included in the primary and secondary efficacy endpoints will be analyzed as exploratory efficacy endpoints. Details for the CGM analyses can be found in Section 6.13.

6.10. Safety Analyses

6.10.1. Extent of Exposure

Duration of exposure to study drug will be summarized based upon eCRF data. The following summary statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (that is, total patient-years of exposure). The number and proportion of patients falling into the following different exposure categories will also be summarized: <14 days (>0 and <14 days), ≥14 and <35 days , ≥35 and <46 days, and ≥46 days.

Patients who complete the study treatment period are required to complete a safety follow-up visit without study drug; and patients who discontinue the IP unplanned are required to discontinue from the study (ITSZ Protocol 7.1).

6.10.2. Adverse Events

Events that are newly reported after the first dose of IP or reported to worsen in severity from baseline will be considered TEAEs. Events that continue during more than 1 study period (lead-in, Treatment, and safety follow-up period) with the same severity will only be counted once for the first study period.

Analyses of AEs will be descriptive and include all data collected during the treatment period. Adverse events during the lead-in period and the safety follow-up period will be provided in a listing.

The MedDRA lowest level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity.

In an overview table, the number and percentage of patients who experienced a TEAE, experienced a serious adverse event (SAE), died due to an AE, and discontinued from study due to an AE will be summarized.

The number and percentage of patients with SAEs and who discontinued from the study due to an AE will be summarized using MedDRA PT nested within SOC if any such events occurred. The number and percentage of patients with TEAEs will be summarized using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

The number and percentage of patients who experienced a SAE including deaths and SAEs temporally associated or preceding deaths will be summarized using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency within SOC. A listing of all SAEs (including data collected during lead in and the safety follow-up period) will also be provided.

The number and percentage of patients who discontinued from study in Treatment period due to an AE will be summarized using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency. A listing of all AEs as reason for study discontinuation will also be provided.

For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender. The number and proportion of patients with at least 1 event for each type of event will also be summarized.

Table ITSZ.6.3 summarizes the planned analyses and the requirement of analysis data for different analysis periods.

Table ITSZ.6.3. Adverse Event Analysis Periods

Analysis Period	Analysis Population	Analysis	IP USE	Treatment
Lead-in Period	Enrolled Population	Listing: All AE including SAEs and discontinuation due to AE	N/A	Humalog
Treatment Period (Titration and Maintenance periods)	Treated Population	AE overview; TEAE by SOC and by PT;; SAE; discontinuation due to AE	Yes	LY900014
Treatment Period (Titration and Maintenance periods) and Safety Follow-up Period	Treated Population	AE overview; TEAE by SOC; SAE; discontinuation from study due to AE;	All data regardless of IP use	LY900014

Abbreviations: AE = adverse event; IP = investigational product; N/A = not applicable/available; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.

6.10.3. Hypoglycemic Events and Other Adverse Events

The analysis plans for the following AEs are discussed in Section 6.10.3.1:

- hypoglycemia
- injection site reaction

These AE analyses will be similar to the TEAE analyses, refer to Table ITSZ.6.3 for the requirement of analysis data for a specific analysis period.

6.10.3.1. Hypoglycemia

Hypoglycemia will be described using the following definitions:

- **Level 1:** Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
- **Level 2:** Glucose <54 mg/dL (3.0 mmol/L)
- **Level 3: Severe hypoglycemia:**

  Participants have altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and require assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. 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 blood glucose concentration.

  - The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
  - All episodes of severe hypoglycemia must be reported as SAEs on the AE eCRF page and on the SAE eCRF page.

Any events of severe hypoglycemia categorized as level 3 per the evaluation of investigators will be collected from ICF signing to Visit 801.

Level 1 and level 2 hypoglycemia will be analyzed based on glucose data from the CGM sensor session. Derivation and analysis of Level 1 and Level 2 hypoglycemia (derived for duration (in minutes) and percentage of time in Level 1 or Level 2) and other CGM endpoints are described in Section 6.13.

Severe hypoglycemia will be collected as AEs in eCRF and all episodes of severe hypoglycemia will be considered as SAEs. Table ITSZ.6.4 provides detailed statistical methods for severe hypoglycemia. Summary statistics will be provided for severe hypoglycemia events from first dose to last dose of IP.

A listing of patients with at least 1 severe hypoglycemia reported (as SAE) from Visit 3 through Visit 801 will be provided.

A list of MedDRA PTs will be used for the narrow search of potential severe hypoglycemia in spontaneously reported AEs. The events identified through the search strategy that are also reported as SAEs will be summarized.

Table ITSZ.6.4. Summary of Analyses for Severe Hypoglycemia

Endpoint	Analysis Period	Statistical Method
Rate of severe hypoglycemic events (per patient per year / 100 years)	Treatment Period	Summary statistics for exposure adjusted rate per year / 100 years (calculated for each patient by total number of events divided by total exposure) will be provided
Incidence of severe hypoglycemic events	Treatment Period	Summary statistics for proportion of patients with severe hypoglycemia will be reported.

6.10.3.2. Injection Site Reaction

The injection site reactions will be searched by MedDRA PTs from all TEAEs. The number and percentage of patients experiencing treatment-emergent injection site reaction will be summarized.

6.10.4. Clinical Laboratory Evaluation

The data from safety laboratory measures will be only collected at Visit 1 for patient eligibility and safety. Therefore, no summary will be provided.

6.10.5. Vital Signs and Other Physical Findings

Post-baseline measurements and change from baseline to post-baseline for vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate) and physical characteristics (weight, BMI) at the scheduled visits will be summarized for patients who have both baseline and at least 1 post-baseline result.

The measurements during the treatment period will be analyzed by MMRM model similar to that for the primary endpoint, i.e., with baseline value of the response variable, visit as fixed factors and patient as the random factor.

6.10.6. Patient Narratives

Patient narratives will be provided for all patients in the study who experience any of the following "notable" events prior to data cutoff for the submission, if any occur during the study:

- deaths
- SAEs
- discontinuations from study (or study drug) due to AEs
- pregnancy

A list of patients who meet the criteria for narratives will be provided.

6.11. Important Protocol Deviations

Important protocol deviations, as defined in the Trial Issue Management Plan (TIMP), will be summarized for the Treated Population. The listing of important protocol deviations for the Treated Population during the entire study, will be provided in the CSR. No per-protocol population is planned for any analyses.

6.12. Interim Analyses and Data Monitoring

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

6.13. CGM Analyses

The analyses described in Section 6.13 will include data collected from first dose of Humalog used during the lead-in period to the last IP used during the treatment period, excluding data (if any) that are collected while patients are temporarily off Humalog or IP.

All CGM outcome variables will only be derived for Visit 3 (baseline) and Visit 14 (endpoint) based upon the CGM data collected from valid CGM days, excluding data (if any) that are collected while patients are temporarily off Humalog during the lead-in period or temporarily off IP during the maintenance period. A valid CGM day to be counted into the calculation for a visit must have at least 70% of the total measures that are supposed to be obtained.

Table ITSZ.6.5 lists all numerical measures for CGM data.

To ensure that the CGM outcome variables are only calculated from CGM session days with sufficient data within the 24-hour, daytime (0600 hours to midnight), or nighttime (midnight to 0600 hours) periods, the following criteria will be used to determine a valid CGM session day to be counted into the calculation for a visit: minimum number of measures per day – at least 70% of the total measures that are supposed to be obtained, i.e., 70% of the 288 measures for the 24-hour period;.

Similarly, for the by-meal outcome variables, the following criteria will be used to determine a valid CGM session day for a visit: minimum number of measures per day – at least 70% of the

total measures that are supposed to be obtained. For example, 70% of the 24 measures for the $iAUC_{0\text{-}2hr}$ after breakfast.

The definition and derivation of these variables are described in detail in Appendix 1.

Table ITSZ.6.5. Outcome Measures of CGM Data

Category	Endpoints	24-Hour	Daytime[a]	Nighttime[b]	By Meal[c]
Efficacy Endpoint: Glucose in the Target Ranges					
	Duration (in minutes) and percentage of time with sensor glucose values within target range 70 to 180 mg/dL [3.9 and 10.0 mmol/L], both inclusive (Primary Efficacy Endpoint)	X	X	X	
Efficacy Endpoint: Incremental AUCs (iAUCs) (after the start of meals)					
	$iAUC_{0\text{-}1hr}$				X
	$iAUC_{0\text{-}2hr}$				X
	$iAUC_{0\text{-}3hr}$				X
	$iAUC_{0\text{-}4hr}$				X
Efficacy Endpoint: Mean Glucose Excursions (after the start of meals) [d]					
	mean sensor glucose excursions 0 to 1 hour				X
	mean sensor glucose excursions 0 to 2 hour				X
	mean sensor glucose excursions 0 to 3 hour				X
	mean sensor glucose excursions 0 to 4 hour				X
Efficacy Endpoint: Hyperglycemia					
	Duration (in minutes) and percentage of time with glucose values >180, 181-250 and >250 mg/dL [10.0, 10.1-13.9 and 13.9 mmol/L]	X	X	X	
Efficacy Endpoint: Daily CGM Data Summary					
	Mean sensor glucose	X	X	X	
	Median sensor glucose	X	X	X	
Efficacy Endpoint: Glucose Variability and Risk Assessment					
Within-Day	CV	X	X	X	
	SD	X	X	X	
	IQR	X	X	X	
Between-Day	CV	X	X	X	
	SD	X	X	X	
Overall[e]	CV	X	X	X	
	SD	X	X	X	
	IQR	X	X	X	

Efficacy Endpoint: Highest Postprandial Glucose					
	Time from start of meal to the highest postprandial glucose level (minutes) within 4 hours after meal(s)				X
	Highest postprandial glucose level within 4 hours after meal(s)				X
	Highest postprandial glucose excursion level within 4 hours after meal(s)				X
Safety Endpoint: Hypoglycemia[f]					
	Duration (in minutes) and percentage of time with sensor glucose values <54, 54-69 and <70 mg/dL [3.0, 3.0-3.8 and 3.9 mmol/L]	X	X	X	X

Abbreviations: AUC = area under curve; CGM = continuous glucose monitoring; CV = coefficient of variation; hr = hour; IQR = interquartile range; SD = Standard deviation.

[a] Daytime: 0600 hours to midnight (06:00:00-23:59:59 on the 24-hour clock).

[b] Nighttime: midnight to 0600 hours (00:00:00-05:59:59 on the 24-hour clock).

[c] By meals: for morning (breakfast), midday (lunch) and evening (dinner) meals and overall (average across all meals). The start time of morning, midday and evening meals are determined as the first entry in the CGM data during [04:00:00, 11:00:00], (11:00:00, 15:00:00] and [17:00:00, 21:00:00], respectively. When calculating time in ranges (target, hypo, hyper) for meals (0 to 1 hour, 0 to 2 hours, 0 to 3 hours and 0 to 4 hours), any data that are collected after the next meal event will be excluded.

[d] Mean sensor glucose measured at different time points (1, 2, 3 or 4 hours) after the start of the meal minus mean sensor glucose at the start of meal

[e] Overall variability refers to the variability calculated based upon all the CGM measurements collected across all valid days for each derivation period

[f] In addition, postprandial hypoglycemia during the following time interval after each meal and overall will also be derived: 0 to 1 hour, 0 to 2 hours, 2 to 4 hours, 0 to 4 hours. The calculation will exclude the data from patients who have had the next meal event before the end of time interval.

The proportion of patients who have achieved the guidance (Battelino 2019) recommended CGM targets of glycemic control (Table ITSZ.6.6) during the lead in period (baseline) and the maintenance period (endpoint) will be summarized.

Table ITSZ.6.6. Guidance Recommended CGM Targets of Glycemic Control

Percentage of time with sensor glucose (24-hour)	**Guidance Recommendation**
target range	
70-180 mg/d.L (3.9-10.0 mmol/L, both inclusive	>70%
hypoglycemia range	
<54 mg/dL (3.0 mmol/L)	<1%
hyperglycemia range	
>250 mg/dL (13.9 mmol/L)	<5%

Other than that, all continuous variables (actual and change from baseline, if applicable) will be analyzed by sing the ANCOVA defined in Section 6.1.

In addition, the following standardized glucose summary reports from the ambulatory glucose profile (AGP) will be generated, based upon all the observed CGM data during the lead in period and the maintenance period, regardless of whether they are collected on valid CGM days:

- 24-hour period at individual patient level
- 24-hour period at the treatment level
- 0 to 4 hours relative to meal starting time, excluding data collected after the next meal event (if any is captured within the interval) at the treatment level
- 0 to 4 hours relative to meal starting time, by meal (breakfast, lunch, and dinner) and by infusion set wear day excluding data collected after the next meal event

6.14. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' Non-SAEs are summarized by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment, the following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced.
- For each SAE, these additional terms are provided for EudraCT:
  - the total number of occurrences causally related to treatment
  - the total number of deaths
  - the total number of deaths causally related to treatment.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment may be excluded if a 5% threshold is chosen. Allowable thresholds include 0% (all events), 1%, 2%, 3%, 4%, and 5%.

- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

Not applicable as this is an open label study.

8. References

Baghurst PA. Calculating the mean amplitude of glycemic excursion from continuous glucose monitoring data: an automated algorithm. *Diabetes Technol Ther*. 2011;13(3):296-302.

Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the International Consensus on Time in Range. *Diabetes Care*. 2019; pii: dci190028.

Clarke W, Kovatchev B. Statistical tools to analyze continuous glucose monitor data. *Diabetes Technol Ther*.

Hirsch IB. Glycemic variability: It's not just about A1c anymore! *Diabetes Technol Ther*. 2005;7(5):780-783.

Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther*. 2005;7(6):849-862.

King AB, Armstrong DU. A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: basal dosing. *J Diabetes Sci Technol*. 2007a;1(1):42-46.

King AB, Armstrong DU. A prospective evaluation of insulin dosing recommendations in patients with Type 1 Diabetes at near normal glucose control: bolus dosing. *J Diabetes Sci Technol*. 2007b;1(1):42-46.

Mazze RS, Strock E, Wesley D, Borgman S, Morgan B, Bergenstal R, Cuddihy R. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. *Diabetes Technol Ther.* 2008;10(3):149-159.

Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. *Diabetes Technol Ther.* 2009;11(suppl 1):S55-S67.

Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes*. 1970;19(9):644–655.

Service FJ, O'Brien PC, Rizza RA. Measurements of glucose control. *Diabetes Care*. 1987;10(2):225-237.

9. Appendices

Appendix 1. Derivation of CGM Variables

9.1. General Derivation Specifications

All CGM outcome variables will only be analyzed for each patient at Visit 3 (baseline) and Visit 14 (endpoint) based upon the CGM data collected from valid CGM days, excluding data (if any) that are collected while patients are temporarily off Humalog during the lead-in period or temporarily off IP during the maintenance period. A valid CGM day to be counted into the calculation for a visit must have at least 70% of the total measures that are supposed to be obtained (Section 6.13).

No missing CGM values will be imputed.

Since the CGM values may not be measured at the exact same time for each day for a specific individual patient, due to device changes or gaps in usage, non-overlapping intervals ('buckets') of 5 minutes over 00:00:00 to 23:59:59 (00:00:00 to 00:04:59, 00:05:00 to 00:09:59, etc.) will be used for any derivations requiring time-matched measurements across days within a visit.

All CGM parameters will be estimated to precision of 1 decimal place, unless stated otherwise. All CGM glucose derivations will be conducted in units of mg/dL and mmol/L.

Only readings collected from valid CGM days while patients are on Humalog in the lead-in period or on IP during the treatment period, will be included in the derived.

9.2. Glucose in Target Ranges, Hypoglycemia or Hyperglycemia

Glucose in target range, hypoglycemia or hyperglycemia will be calculated as the average value of percentage of time within a glucose range (target, hypo- or hyperglycemia ranges) on all valid CGM days during that visit.

The percentage of time within a glucose range (target, hypo- or hyperglycemia ranges) will be calculated as the number of observations within the specified range divided by the number of observations in the time interval (eg, 24-hour period). The duration (in minutes) within the glucose range will then be calculated as the percentage of time within the glucose range times the length of the period (24 hour, 18 hour, and 6 hour, for the periods of 24-hour, daytime or nighttime, respectively).

For example, if a patient had a total of 15 observations with glucose values <70 mg/dL (3.9 mmol/L) out of a total of 288 observations recorded during the 24-hour period in a valid CGM day at Visit 3, the percentage of time spent in hypoglycemia during the 24-hour period for this patient at that valid CGM day at Visit 3 will be calculated as 15/288 = 5.2%. The duration (in minutes) with hypoglycemia (glucose value <70 mg/dL [3.9 mmol/L]) during the 24-hour period for this patient at that valid CGM day at Visit 3 will be calculated as the percentage times 1440, (ie, 15/288*1440 = 75.0 minutes). Then derive the CGM outcome for each visit by averaging across all valid CGM days at that visit.

The percentage and duration in ranges within 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after meals will also be derived.

9.3. Incremental Area under the Glucose Curve (iAUC)

$iAUC_{0\text{-}T}$ will be calculated as the average value of iAUC on all valid CGM days during that visit with sufficient data to calculate the $iAUC_{0\text{-}T}$ (Section 6.13). For each day, $iAUC_{0\text{-}T}$ will be calculated as the sum of areas of all individual trapezoids within the time frame according to the formula:

$$i\text{AUC}_{0-\text{T}} = \sum_{i=1}^{k} Ai = \sum_{i=1}^{k} \frac{(G_i - G_0) + (G_{i-1} - G_0)}{2} \boldsymbol{\Delta t_i}$$

where A_i is area of the respective trapezoid, G_i is glucose concentration at a particular time, G_0 is the starting glucose concentration before the start of the meal, is the time interval between consecutive CGM values, which should be always 5 minutes unless missing data occur, and *k* is the total number of intervals within the time frame 0-T. If the intermediate time points are missing, the next available time point will be used in calculating the trapezoid area. Also since it is possible that $G_i < G_0$ or $G_{i-1} < G_0$, A_i could also be negative. G_0, the starting glucose concentration, will be calculated as the average of the CGM values in the time window [-19, 0] mins relative to the start of the meal (at most 3 CGM values); G_k, the last glucose concentration, is defined as the average of the CGM values in the window [0, +14] minutes relative to the last time point of the time frame (at most 2 CGM values). For example, to calculate $iAUC_{0\text{-}2hr}$ after the start of breakfast, G_k will be the average of the CGM values in the window [0, +14] minutes relative to the 2 hours after the start of breakfast. The derivation of each $iAUC_{0\text{-}T}$ will require that G_0 and G_k values are both available. The derivation $iAUC_{0\text{-}T}$ on a specific infusion set wear day, requires that time 0 and time T fall on the same infusion set wear day,but it is acceptable that the CGM measures in the window [-19,0] for G_0 and [0+14] for G_T fall on the previous or the next infusion set wear day.

9.4. Mean Sensor Glucose Excursions

Mean sensor glucose excursions in a postmeal time interval (0-1 hr, 0-2 hr, 0-3 hr or 0-4 hr) will be calculated by averaging all excursion values within the time interval. Excursions will be derived by subtracting glucose values by the starting glucose concentration, which is the average of the CGM values in the time window [-19, 0] mins relative to the start of the meal (at most 3 interstatial glucose measures).

9.5. Glucose Variability

Glycemic variability will be evaluated using the notation below:

i represents a time point within a time period (a 24-hour period, daytime or nighttime)

n represents the number of time points within the time period

k represents a day within a visit

m represents number of days CGM is performed at a visit

$BG_{k,i}$ represents the glucose value at time point *i* on day *k.*

9.5.1. Within-Day Variability

For variables assessing within-day variability, first determine the variability within each day, then average across days within a visit.

Within-day glucose standard deviation (SD) (Hirsch 2005; Rodbard 2009):

$$SD = \frac{1}{m}\sum_{k=1}^{m} \mathrm{SD}_k = \frac{1}{m}\sum_{k=1}^{m} \sqrt{\frac{\sum_{i=1}^{n} (BG_{k,i} - \left\{\frac{\sum_{i=1}^{n} BG_{k,i}}{n}\right\})^2}{n-1}}$$

Within-day glucose coefficient of variation (CV) (Clarke 2009):

$$CV = \frac{1}{m}\sum_{k=1}^{m} CV_k = \frac{1}{m}\sum_{k=1}^{m} \frac{SD_k}{(\frac{\sum_{i=1}^{n} BG_{k,i}}{n})} \times 100$$

Inter-quartile range (IQR) (Mazze et al. 2008):

$$IQR = \frac{1}{m}\sum_{k=1}^{m} IQR_k = \frac{1}{m}\sum_{k=1}^{m} (75\text{th} - 25\text{th percentile of all BG values on day k})$$

9.5.2. Between-Day Variability

For variables assessing between-day variability, first determine the variability for each time points across days within a visit then average across all time points.

Between-day glucose standard deviation (SD) (Rodbard 2009):

$$\mathrm{SD} = \frac{1}{n}\sum_{i=1}^{n} SD_i = \frac{1}{n}\sum_{i=1}^{n} \sqrt{\frac{\sum_{k=1}^{m} (BG_{k,i} - \left\{\frac{\sum_{k=1}^{m} BG_{k,i}}{m}\right\})^2}{m-1}}$$

Between-day glucose coefficient of variation (CV):

$$CV = \frac{1}{n}\sum_{i=1}^{n} CV_i = \frac{1}{n}\sum_{i=1}^{n} \frac{SD_i}{\left(\frac{\sum_{k=1}^{m} BG_{k,i}}{m}\right)} \times 100$$

9.5.3. Overall Variability

The CV, SD and IQR will be calculated using the standard formulas across collected across all valid days for time interval in each randomized treatment period.

9.6. Daily CGM Data Summary

For daily CGM summary variables, first determine the values within each day, then average across days within a visit. The hourly mean glucose will be calculated as the mean across all CGM values collected, based on actual local time for the subject.

9.7. AUC

Area under the curve (AUC) during a period (24-hour, daytime, or nighttime) will be calculated using the standard linear trapezoidal method as defined previously in Section 9.3, by multiplying the sum of trapezoids by (the length of the period)/(the length of the period - total length of gaps that are not counted into the calculation of the AUC).

9.8. Highest Postprandial Glucose

9.8.1. Time to the highest postprandial glucose within 4 hours after Meals

Time from start of meal to the highest postprandial glucose level will be calculated as the time from start of meal to the maximum glucose value within 4 hours after meals, excluding the data from patients who have had the next meal event. If there are multiple time points with the maximum glucose value, then the earliest time will be used.

9.8.2. Highest Postprandial Glucose Level within 4 hours after Meals

Highest postprandial glucose level excursions within 4 hours after meals, will be calculated as the maximum glucose value during 0 to 4 hours after start of meal, excluding the data from patients who have had the next meal event.

9.9. Other

The duration of each episode of hypoglycemia will be calculated as stop time – start time.

Leo Document ID = 2af4a1db-2508-40af-a5a4-6ab4e66add38

Approver: PPD

Approval Date & Time: 05-Oct-2020 13:39:47 GMT

Signature meaning: Approved