Statistical Analysis Plan: I8B-MC-ITSM (V3)

Evaluation of LY900014 in a Medtronic Pump

NCT03760640

Approval Date: 29-Oct-2019

1. Statistical Analysis Plan: I8B-MC-ITSM: Evaluation of LY900014 in a Medtronic Pump

LY900014

Study I8B-MC-ITSM is a prospective, randomized, double-blind, outpatient, single-center, 2-treatment, crossover, active-controlled study conducted in patients with type 1 diabetes currently using an external CSII pump.

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Protocol I8B-MC-ITSM
Phase II

Statistical Analysis Plan version 1 electronically signed and approved by Lilly on 19-Dec-2018
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Statistical Analysis Plan version 3 electronically signed and approved by Lilly on date below

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first patient visit. Version 1 is based on the Protocol I8B-MC-ITSM (ITSM) approved on 24 October 2018.

Statistical Analysis Plan (SAP) Version 2 was approved prior to the first patient visit. Version 2 is based on the Protocol I8B-MC-ITSM (ITSM) (a) amended on 24 January 2019. The main changes are listed below:

- Updated the study design plot according to the amended study design;
- Added a listing to describe any significant safety event that occurs during the pilot safety assessment;
- Changed "treatment group" to "treatment" according to the amended protocol;
- Changed the baseline observations for HbA1c and 1,5 AG from "Visit 4 prior to the first dose of IP" to "Visit 4 prior to or on the date of the first dose of IP";
- Changed the baseline observations for insulin doses and percentage of time (per week) spent in Auto Mode from "Visit 4" to "Last of Visits 2-4";
- Changed the baseline observations for treatment-emergent adversent events during the safety follow-up from "After first dose of IP and Prior to last dose of IP in the 8-Week Treatment Period" to "Prior to last dose of IP in the 8-Week Treatment Period";
- Added some clarification language for treatment comparisons in hypoglycemia analyses. "Treatment comparisons for severe hypoglycemia will be based upon the data collected for 0-4 weeks of each treatment period. Treatment comparisons for other categories of hypoglycemia will be only based upon the data collected for 2 to 4 weeks.";
- Changed "average glucose excursion" to "mean sensor glucose excursion" to be consistent with the protocol exploratory objective. Similarly, changed "average glucose level" and "hourly average glucose level" to "mean sensor glucose level" and "hourly mean sensor glucose level";
- Added "$iAUC_{0\text{-}3hr}$" and "$iAUC_{0\text{-}4hr}$" in the CGM outcome measures.

Statistical Analysis Plan (SAP) Version 3 was approved prior to the database lock. The main changes are listed below:

- Removed the analyses of insulin doses, pump factors, weight, and vital signs for the lead-in period given the short duration and the fact that there was no titration done
- Added the definition of baseline and post-baseline observations for the analysis of insulin doses by infusion set wear day
- Added the 7information of SMBG/CGM before the correction bolus in the listing of infusion set changes
- Added patient narrative

- Added more derivation details for CGM outcome variables
- Removed the analyses of hyperglycemia as measured by CGM>300 mg/dL and added the analyses of CGM (181to 250 mg/dL and 54 to 69 mg/dL) to align with categories of hyperglycemia recommended in recent international consensus guidance (Battelino 2019)
- Added R Shiny plots as part of CGM data presentation
- Added details on analyses of unplanned infusion set changes

4. Study Objectives

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

Table ITSM.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
1. To compare LY900014 and Humalog with respect to the percentage of time with sensor glucose values within range (70 to 180 mg/dL)	1. Percentage of time with sensor glucose values between 70 and 180 mg/dL (both inclusive), during the last 2 weeks of each 4-week treatment period
Secondary	
2. To compare LY900014 with Humalog with respect to the mean sensor glucose	2. Mean sensor glucose value (mg/dL), during the last 2 weeks of each 4-week treatment period
3. To compare LY900014 and Humalog with respect to the percentage of time spent in Auto Mode	3. Percentage of time (per week) spent in Auto Mode, during the last 2 weeks of each 4-week treatment period
4. To compare LY900014 with Humalog with respect to the percentage of time with sensor glucose values in hypoglycemic glucose ranges	4. Percentage of time with sensor glucose values <54 mg/dL during the last 2 weeks of each 4-week treatment period
5. To compare LY900014 and Humalog with respect to the rate of severe hypoglycemic events	5. Rate (events/patient/100 years) of severe hypoglycemic events during each 4-week treatment period
6. To compare LY900014 and Humalog with respect to the rate and incidence of documented hypoglycemia	6. Rate (events/patient/year) and incidence (percent of patients with events) of documented hypoglycemic events, during the last 2 weeks of each 4-week treatment period
7. To compare LY900014 and Humalog with respect to total daily dose	7. Mean total daily bolus insulin dose and mean total daily basal insulin dose during the last 2 weeks of each 4-week treatment period
Tertiary/Exploratory	
8. To compare the safety of LY900014 and Humalog	8. Adverse events and vital signs
9. To compare LY900014 and Humalog with respect to the percentage of time with sensor glucose values within range (70 and 140 mg/dL)	9. percentage of time with sensor glucose values between 70 and 140 mg/dL (inclusive), during the last 2 weeks of each 4-week treatment period
10. To compare LY900014 and Humalog with respect to the rate and incidence of unplanned infusion set changes	10. Rate (events/patient/30 days) and incidence of unplanned infusion set changes by reason (Pump occlusion alarm, Suspected infusion set occlusion (unexplained high BG), Infusion site reaction (pain, redness or swelling at infusion site), Infusion set problem (infusion set kinked, pulled out, leaking, reservoir empty, etc.), during the 4-week treatment period
11. To compare LY900014 and Humalog with respect to the percentage of time with sensor glucose values in hyperglycemic glucose ranges	11. Percentage of time with sensor glucose values >180 mg/dL and >250 mg/dL, during the last 2 weeks of each 4-week treatment period

Objectives and Endpoints

Objectives	Endpoints
12. To compare LY900014 and Humalog with respect to the 1-hour postprandial sensor glucose excursions	12. Mean 1-hour postprandial sensor glucose excursions (mean sensor glucose measured 1 hour after the start of the meal minus mean sensor glucose at the start of meal) after breakfast, during the last 2 weeks of each 4-week treatment period
13. To compare LY900014 and Humalog with respect to the within-patient sensor glucose variability	13. Coefficient of variation (CV) (standard deviation/mean) of sensor glucose values, during the last 2 weeks of each 4-week treatment period
14. To evaluate HbA1c of LY900014 and Humalog	14. Summary statistics of actual and change of HbA1c during each 4 week treatment period
15. To evaluate 1,5-AG of LY900014 and Humalog	15. Summary statistics of actual and change of 1,5-AG during each 4-week treatment period
16. To compare LY900014 and Humalog with respect to the factors affecting dosing in pumps	16. Actual and change from baseline in factors affecting dosing in pump (breakfast CR, AIT, breakfast ISF), during the 4-week treatment period

Abbreviations: 1,5-AG = 1,5 Anhydroglucitol; AIT = active insulin time; BG = blood glucose; CR = carb ratio; HbA1c = hemoglobin A1c; ISF = insulin sensitivity factor.

5. Study Design

5.1. Summary of Study Design

Study ITSM is a prospective, randomized, double-blind, outpatient, two-center, 2-treatment, crossover, active-controlled study conducted in patients with type 1 diabetes (T1D) currently using an external continuous subcutaneous insulin infusion (CSII) pump. In the 2 treatments, LY900014 and Humalog will be delivered via the Medtronic MiniMed 670G system with SmartGuard™ technology using AutoMode. In this study, patients will be required to use the Auto Mode insulin delivery function as much as possible.

The study is designed to compare LY900014 and Humalog with respect to the duration of time glucose values are within range (70 to 180 mg/dL, both inclusive). The study includes a 1-week screening period and a 2-week lead-in period followed by a 2-period crossover, each period consisting of 4 weeks of treatment, and a 2-week post-treatment safety follow-up.

Following the lead-in period, a 3-day pilot safety assessment will be conducted for the first 10 patients randomized. This pilot safety assessment will determine if the control algorithm in the Medtronic 670G pump can be used safely in patients receiving LY900014.

Figure ITSM.5.1 illustrates the study design.

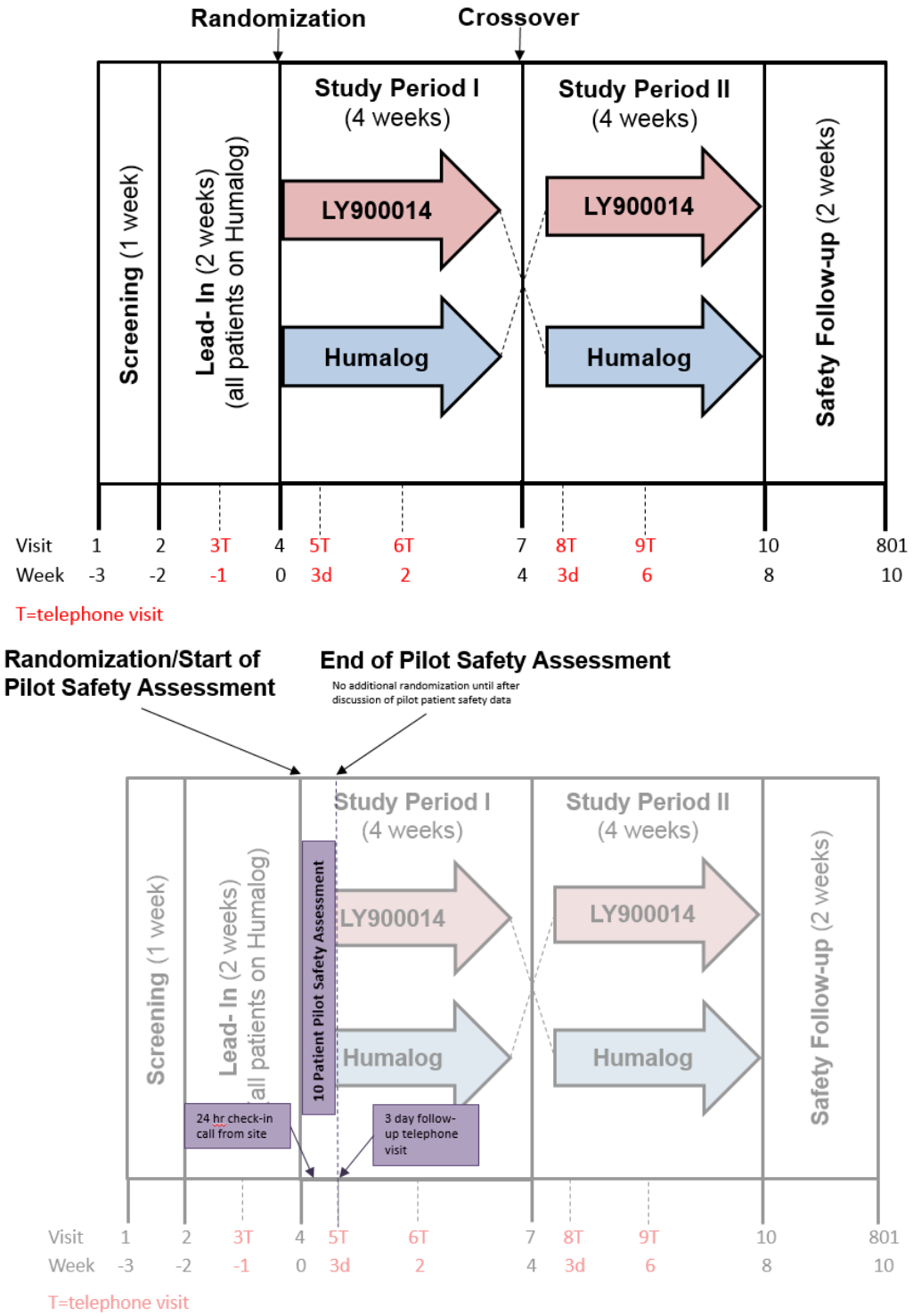

Figure ITSM.5.1. Illustration of study design for Clinical Protocol I8B-MC-ITSM.

Patients who need to discontinue from study treatment will also be discontinued from the study. Please refer to Protocol Sections 8.1 and 8.2.

CareLink Personal Software allows patients to upload data from their insulin pump, continuous glucose monitoring (CGM) device, and blood glucose (BG) meter into a web-based program. Patients can see detailed reports that help them better understand their BG control and uncover patterns missed by meters and logbooks. Patient information is stored and will allow the investigator or designee to access to it via CareLink Pro Software.

In this study, patients will upload data to CareLink Personal remotely on a weekly basis. The investigator or designee will review patient uploaded CareLink reports weekly for use in clinical management of the patient. Specified data from CareLink reports will be entered into electronic case report forms (eCRFs) per the Schedule of Activities. In this document, these data are referred to as the CareLink report data.

In addition, raw data from CareLink Personal will be downloaded by the site as .csv files. The data in these files will be used for the analyses of interstitial glucose (including the primary objective) and pump-related safety outcomes. In this document, these files are referred to as the CareLink raw data.

5.2. Determination of Sample Size

Approximately 42 patients will be randomized in order that approximately 36 patients complete the study.

Assuming that a standard deviation (SD) of between-period differences of 10% and a 2-sided alpha level of 0.10, 36 completers will provide approximately 90% power to detect a 5% difference between LY900014 and Humalog, in the percentage of time with SG (Sensor Glucose) values from 70 to 180 mg/dL (inclusive), during the last 2 weeks of each 4-week treatment period.

Assuming a 12% dropout rate after randomization, approximately 42 patients (21 patients in each sequence) will need to be randomized.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment and complete the lead-in period will be randomized to double-blind treatment at Visit 4. Assignment to treatment sequences will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

Patients will be randomized to 1 of the 2 treatment sequences in a 1:1 ratio:

Sequence A: LY900014 $\rightarrow$ Humalog
Sequence B: Humalog $\rightarrow$ LY900014

Stratification will be by hemoglobin A1c (HbA1c) stratum ($\leq$7.0%, >7.0% at Visit 1) and percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization ($\leq$75%, >75%).

Patients will begin using a new reservoir and infusion set prior to leaving the investigative site at Visits 2, 4, 7, and 10. Patients will change the pump reservoir and infusion set every 3 days unless a change is required due to failure of the infusion set.

The IWRS will be used to assign all study treatment during the study, including Humalog during the lead-in period. The IWRS will be used to assign vials containing double-blind investigational product (IP) to each patient randomized to the sequence of treatments. Site personnel will confirm that they have located the correct vials by entering a confirmation number found on the vials into the IWRS.

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 (CSR). Additional exploratory analyses of data will be conducted, as deemed appropriate.

For purposes of analysis, the following populations are defined in Table ITSM.6.1:

Table ITSM.6.1. Patient Populations

Population	Description
Entered	All patients who give informed consent.
Enrolled	All patients who receive at least 1 dose of open-label Humalog in the 2-week lead-in period.
Randomized	All patients who are randomly assigned to study treatment at Visit 4 and receive at least 1 dose of the randomly assigned IP. Treatment will be defined on the basis of the treatment the patients are assigned to.
Pilot	All patients in the pilot safety assessment.

Unless otherwise specified, all efficacy and safety analyses will be conducted on the Randomized Population. Analyses of adverse events (AEs) will include all data collected during the course of the entire 4-week treatment period for each treatment regardless of IP use. Analyses of hypoglycemia and CGM measures will be conducted using the data from first dose to last dose of IP in each 4-week treatment period, and due to the crossover design, treatment comparisons will be based upon the derived outcome variables for Week 2 to 4 in each 4-week treatment period. Analyses of the CareLink report data that are transferred to eCRF (eg, percentage of time spent in Auto Mode, total daily doses during the last 2 weeks) will include all data collected, regardless if patients are temporarily off pump or IP during the 2 weeks or not. Pump-related safety analyses (eg, infusion set changes) will exclude data (if any) that are collected while patients are temporarily off pump or off IP. For analyses of CGM, insulin doses and meal information by infusion set wear day, only data from the infusion sets with ≥60 hours (2.5 days) of wear will be included so that adequate data can be used for by-day (Day 1, Day 2, and Day 3) comparison. Data collected during the safety follow-up period will not be used for comparisons between treatments.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.10, and confidence intervals (CIs) will be calculated at 90%, 2-sided.

Treatment comparisons will be performed for the primary objective (Section 6.9.1) at the full significance level of 0.10. No multiplicity adjustment will be made for secondary and exploratory objectives.

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 after Visit 2 to Visit 4
- 4-Week of Each Randomized Treatment Period while on IP – from first dose to last dose of IP in each 4-week randomized treatment period (Period I and Period II)
- 4-Week of Each Randomized Treatment Period Regardless of IP use – from the beginning to the end of each 4-week randomized treatment period (including all data regardless of IP use)
- Week 2 to 4 of Each Randomized Treatment Period while on IP – last 2 weeks of each 4-week randomized treatment period before the last dose of IP
- Week 2 to 4 of Each Randomized Treatment Period Regardless of IP – last 2 weeks of each 4-week randomized treatment period (including all data regardless of IP use)
- Safety Follow-up Period – Visit 801

Table ITSM.6.2 describes the rules for determining the patient population, baseline, and postbaseline observations for the different analysis periods. The data in the lead-in and the safety follow-up visit, if summarized, will be for overall, not by treatment.

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 randomized treatment period (Period I or Period II), then postbaseline data measured at or prior to that office visit will be considered as data on IP for the current randomized treatment period.
- for data collected as running records with an exact date and/or time stamp such as hypoglycemia entries where the date and time of the measures is not tied with the date of an office visit, postbaseline data with date and time ≤ (last study drug dose date and time) will be considered as data on IP for the current randomized treatment period.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least squares (LS) means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 90% CIs for the treatment differences, along with the p-values for the treatment comparisons.

Unless otherwise specified, a restricted maximum likelihood based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. The longitudinal observations for both treatment periods will be included in the analysis. The model will include the fixed class effects of treatment, period, sequence, strata (HbA1c [≤7.0%, >7.0%] and percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization [≤75%, >75%]), and the continuous, fixed covariate of baseline value. The

Kenward-Roger approximation will be used to estimate denominator degrees of freedom. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, a covariance structure of compound symmetry without heterogeneous variances will be used. If the model still does not converge, strata may be removed from the model. Significance tests will be based on LS means and Type III tests. SAS PROC MIXED will be used to perform the analysis.

For categorical measures (such as incidence of AEs), summary statistics will include sample size, frequency, and percentages. Prescott's exact test will be used for treatment comparisons, unless otherwise specified. Since Prescott's exact test is essentially a Fisher's exact test on the preference score and treatment sequence, if all events occurred in the same treatment sequence, p-values from Prescott's test will not be calculated.

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 ITSM.6.2. 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 (Overall[a] only)			
TEAEs	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 4 date if the dose date is missing)
4-Week of Each Randomized Treatment Period While on IP (from first to last dose of IP in each 4-week randomized treatment period)			
Unplanned infusion set changes by reason (pump occlusion alarm; unexplained high BG; infusion site reaction (pain, redness or swelling at infusion site), or infusion set problem (infusion set kinked, pulled out, leaking, reservoir empty, etc.))	Randomized Population	From first to last dose of open-label Humalog, excluding data (if any) that are collected while patients temporarily are off pump or off open-label Humalog	From first to last dose of IP in each randomized treatment period (Period I and Period II), excluding data (if any) that are collected while patients temporarily are off pump or off IP

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
Time interval until infusion set change	All patients in the Randomized Population with a baseline and a post-baseline observation	From first to last dose of open-label Humalog, excluding data (if any) that are collected while patients temporarily are off pump or off open-label Humalog	From first to last dose of IP in each randomized treatment period (Period I and Period II), excluding data (if any) that are collected while patients temporarily are off pump or off IP
Hypoglycemia events	Randomized Population	From first to last dose of open-label Humalog	Visits 4, 5, 6, 7, 8, 9 and 10 that fall between first and last dose of IP in each randomized treatment period (Period I and Period II). More detailed analysis period can be found in Section 6.10.4.
HbA1c summary statistics	All patients in the Randomized Population with a baseline and at least one post-baseline observation while on IP	Last value of Visits 1-4 prior to or on the date of the first dose of IP	Visits 7 and 10 while on IP[d]
1,5-AG	All patients in the Randomized Population with a baseline and at least one post-baseline observation while on IP	Visit 4 prior to or on the date of the first dose of IP	Visits 7 and 10 while on IP
Pump factors - CR, ISF, and AIT[b]	All patients in the Randomized Population with a baseline and at least one post-baseline observation	Last value of Visits 2-4 prior to or on the date of the first dose of IP	Last observation 1 day prior to Visit 7 and last observation 1 day prior to Visit 10 prior to last dose in IP of each randomized treatment period (Period I and Period II) excluding data (if any) that are collected while patients temporarily are off pump or off IP

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
4-Week of Each Randomized Treatment Period Regardless of IP use (from randomization to Week 4 of each randomized treatment period regardless of IP use)			
TEAEs	Randomized Population	Prior to first dose of randomized IP (or Visit 4 if the dose date is missing)	Each 4-week randomized treatment period regardless of IP use
Weight and vital signs	All patients in the Randomized Population with a baseline and a post-baseline observation	Last of Visits 2-4	Visits 7 and 10 regardless of IP use
Week 2-4 of Each Randomized Treatment Period while on IP			
CGM outcome variables	All patients in the Randomized Population (with a baseline and a post-baseline observation for continuous variables, unless otherwise specified[c])	From first to last dose of open-label Humalog, excluding data (if any) that are collected while patients temporarily are off pump or off open-label Humalog	From first to last dose of IP in each randomized treatment period (Period I and Period II), excluding data (if any) that are collected while patients temporarily are off pump or off IP
Week 2-4 of Each Randomized Treatment Period Regardless of IP			
Basal, bolus, and total insulin doses, bolus/total insulin dose ratios[d]	All patients in the Randomized Population with a baseline and a post-baseline observation	Last of Visits 2-4	Visits 7 and 10 regardless of IP use
Basal, bolus, and total insulin doses, bolus/total insulin dose ratios by infusion set wear day, by meal, and by infusion set wear day and meal[e]	All patients in the Randomized Population with a baseline and a post-baseline observation	Last of Visits 2-4	Last observed value before/at Visit 7 and before/at Visit 10 regardless of IP use
Percentage of time (per week) spent in Auto Mode[f]	All patients in the Randomized Population with a baseline and a post-baseline observation	Last of Visits 2-4	Visits 7 and 10 regardless of IP use
Safety Follow-Up Visit (Overall[a] Only)			
TEAEs	All patients in the Randomized Population who enter the safety follow-up period	Prior to first dose of randomized IP (or Visit 4 if the dose date is missing)	From the date of the last visit of the 8-Week treatment period + 1 day to the end of study
Weight and vital signs	All patients in the Randomized Population who enter the safety follow-up period	Last of Visits 2-4	Visit 801

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; AIT = active insulin time; BG = blood glucose; CGM = continuous glucose monitoring; CR = carb ratio; eCRFs = electronic case report forms; HbA1c = hemoglobin A1c; IP = investigational product; ISF = insulin sensitivity factor; TEAE = treatment-emergent adverse event.

[a] "Overall" means that data will be summarized in total and no by-treatment summary or statistical analysis will be included.

[b] The pump settings that patients started with in each treatment period (lead-in, Period I and Period II) are captured in the eCRF. Changes during the study are captured in CareLink raw data. The pump settings that patients ended up within each treatment period will be the last observed value from the two data sources 1 day prior to the last office visit.

[c] Not required for the duration of hypoglycemic episode because it is possible that some patients may not have any hypoglycemic event during the lead-in period to be used as baseline values.

[d] Mean insulin doses (mean total daily basal and mean total daily bolus) during the last 1 week for Visit 2 and during the last 2 weeks for Visits 4, 7, and 10 from the CareLink report will be entered into eCRFs. 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.

[e] Calculated from the CareLink raw data by adding up all insulin doses that fall into the specified time interval (e.g., a specific infusion set wear day), regardless of whether the pump is in Auto Mode or not.

[f] Captured in the eCRF as "percentage of time spent in Auto Mode per week for the past 1 week" at Visit 2 and as "percentage of time spent in Auto Mode per week for the past 2 weeks" at other visits.

6.2. Adjustments for Covariates

Stratification factors of this study include HbA1c stratum (≤7.0%, >7.0%) and percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization (≤75%, >75%). Stratification factors will be entered into the IWRS for randomization and also collected in the database by Carelink raw data or central laboratory. The analysis models will use the stratification factors as collected in the database (e.g HbA1c stratum according to the central lab at baseline and percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization calculated from the CareLink raw data).

Other analyses will include the stratification factors as noted in Sections 6.9 to 6.10.

6.3. Handling of Dropouts or Missing Data

For continuous variables, missing data will be addressed by using a MMRM analysis for continuous longitudinal variables. 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

Treatment comparisons will be performed for the primary objective (Section 6.9.1) at the full significance level of 0.1. No multiplicity adjustments will be made for secondary and exploratory objectives.

6.5. Patient Disposition

Patient disposition will be displayed in a flowchart showing the number of patients entered, enrolled, randomized, and discontinued across the lead-in period, Period I, and Period II.

Frequency counts and percentages of the Randomized Population completing and discontinuing from the study will be presented for overall and by each treatment sequence and period. Reasons for discontinuation from the study will be summarized for overall and by treatment sequence and period. Reasons for discontinuation from the study at Visit 801 will be summarized by treatment sequences.

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 and from the treatment 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 Randomized Population, including the following variables but not limited to: investigator ID, patient ID, date of signature of informed consent form, treatment sequence assignment, randomization date, first and last dose date in each treatment period (lead-in, Period I, and Period II).

6.6. Patient Characteristics

A summary table for overall and by treatment sequence will be generated for patient characteristics at study entry using the Randomized Population. The following variables will be included but not limited to: age, age groups (<40 and ≥40 years, and <65, ≥65 to <75, ≥75 to <85, ≥85 years), sex, country, ethnicity, race, height, weight, body mass index (BMI), BMI groups (<25, ≥25 to <30, ≥30 to <35, and ≥35 kg/m^2). No statistical comparisons between treatment sequences will be performed. 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, duration of CSII use, duration of 670G use, infusion set cannula length (6 mm or 9 mm), the type of rapid-insulin at study entry, the pump speed at study entry and baseline, total daily dose at study entry, percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization at study entry, HbA1c at study entry and baseline, and HbA1c stratum at baseline.

A listing of patients whose stratification factor value entered into the IWRS (for treatment assignment) is different from the clinical database will also be provided.

The total daily insulin dose for the last 3 days prior to screening will be entered into the eCRF. The dose at study entry will be calculated as the mean of the doses for the last 3 days prior to the visit. Doses will be summarized in U and U/kg. Total daily insulin dose will also be presented by the definitions in protocol exclusion criterion #19 (≤100 U, >100 U).

For the Randomized 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.

All baseline measures will be summarized for overall and by treatment sequence. No statistical comparison between treatment sequences will be performed given the small sample size of this study.

6.7. Treatment Compliance

No analysis for treatment compliance is planned for this study.

6.8. Concomitant Therapy

Concomitant medications will be summarized and compared between treatments using Prescott's exact test for the Randomized Population during the 2 randomized treatment periods (Period I and Period II). 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 compare LY900014 and Humalog with respect to the percentage of time with SG values within range (70 to 180 mg/dL, both inclusive), during the last 2 weeks of each 4-week treatment period. The analysis model (MMRM) and selection of covariance structure are described in Section 6.1.

The primary analyses will be tested at the full significance level of 0.10, using data collected from the Randomized Population, while patients are on IP (ie, from first dose to last dose) and on pump.

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 Randomized Population. Details for the CGM analyses are described in Section 6.13.

For the following secondary efficacy endpoints during the last 2 weeks of each 4-week treatment period, an MMRM model similar to that for the primary endpoint 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 /mean total daily insulin dose ratios (%)
- actual and change from baseline in percentage of time (per week) spent in Auto Mode, during the last 2 weeks of each 4-week treatment period
- actual and change from baseline in percentage of time with sensor glucose values <54 mg/dL as measured by CGM

In addition, the longitudinal observations of actual and change during each 4-week treatment period in HbA1c and 1,5-AG will be summarized by period and by treatment sequence. No treatment comparison will be conducted.

To assess the insulin doses over the course of 3 days of continuous infusion, the mean total daily basal and mean total bolus doses during the last 2 weeks of the lead-in and each 4-week treatment period, will be derived based upon the CareLink raw data collected on Day 1, Day 2, and Day 3 of infusion set wear and summarized by treatment. The insulin doses will also be summarized by infusion set wear day, and by both infusion set wear day and meal (0 to 4 hours after the start of meals, excluding data collected after the next meal for the current meal). Only data from the infusion sets with ≥60 hours of wear will be included in these doses analyses by infusion set wear day. The treatment comparison will be conducted using an MMRM model similar to that for the primary endpoint.

Before the database lock, it was identified that 1 patient had to replace the pump in the middle of the study and Auto Mode was unavailable for at least 48 hours, and thus data from this patient will be excluded from analysis of percentage of time (per week) spent in Auto Mode.

6.9.3. Exploratory Efficacy Analyses

An MMRM model similar to that for the primary endpoint will be used to analyze actual and change from baseline in pump factors that affect insulin dosing.

The initial settings for pump factors, including carb ratio (CR), active insulin time (AIT), and insulin sensitivity factor (ISF), will be captured in eCRF at Visit 2, Visit 4 and Visit 7 for the lead-in, Period I and Period II, respectively. Any changes during any treatment period will be captured in the CareLink raw data and associated to meals for CR and ISF. A listing of pump factors will be provided, including data collected at Visit 2 and changes captured in the CareLink raw data.

Actual and change from baseline in pump factors, including CR by meal, ISF by meal and AIT, will be summarized and compared between LY900014 and Humalog using an MMRM models as specified in Section 6.1. Only postbaseline measures at Visit 7 and Visit 10 will be included for analyses.

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 CRF 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: <7 days (>0 and <7 days), ≥7 and <14 days , ≥14 and <28 days, and ≥28 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 (ITSM Protocol 8.1 to 8.2).

6.10.2. Adverse Events

Events that are newly reported after the first dose of rapid-acting insulin provided as study drug (ie, open-label Humalog used during the lead-in period or IP used during each of the two 4-week randomized treatment periods) or are reported to worsen in severity from baseline (defined in Table ITSM.6.2 for each specific study period) will be considered treatment-emergent adverse events (TEAEs). Events that continue during more than 1 study period (lead-in, Period I, Period II) with the same severity will only be counted once for the first study period.

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. For events occurring on the day of first dose of blinded insulin provided in this study during each treatment period (lead-in, Period I and Period II), the CRF-collected flag will be used to determine whether the event started or worsened post-treatment, and/or the treatment of which period the AE should be assigned.

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. Prescott's exact test will be performed for treatment comparison.The number and percentage of patients with TEAEs will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. As an additional table, the percentages of patients with TEAEs will be summarized by treatment using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency in total group. Statistical comparisons will be applied at both the SOC and PT levels. Prescott's exact test will be performed for treatment comparison.

The number and percentage of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT nested within SOC. For each patient and TEAE on each treatment, the maximum severity for the MedDRA PT is the maximum postbaseline severity

observed from all associated LLTs mapping to the MedDRA PT during the corresponding randomized treatment period for the specified treatment. No statistical comparison between treatments will be conducted.

The number and percentage of patients who experienced a SAE including deaths and SAEs temporally associated or preceding deaths will be summarized by treatment 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 the safety follow-up period) will also be provided.

The number and percentage of patients who discontinued from study in Period I and Period II due to an AE will be summarized by treatment 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.

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

Table ITSM.6.3. Adverse Event Analysis Periods

Analysis Period	Analysis Population	Analysis	IP USE	Treatment
Lead-in Period	Enrolled Population	AE overview; TEAE by PT; SAE, discontinuation due to AE	N/A	Open-label Humalog
Treatment Period (0-8 Weeks)	Randomized Population	AE overview; TEAE by PT nested within SOC and by PT; TEAEs by maximum severity; SAE; discontinuation due to AE; other notable AEs	All data regardless of IP use	LY900014, Humalog
Safety Follow-up Period	All patients in the Randomized Population who enter follow-up period	TEAE by PT	All data	Overall[a]

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.

[a] overall means that data will be summarized in total and no by-treatment summary or statistical analysis will be included.

6.10.3. Deaths and Other Serious Adverse Events

The listing of all deaths by patient for the Enrolled Population will be provided as part of the SAE listing, regardless of the investigator's or the sponsor's judgment about causality. Each listing will include study ID, investigator ID, patient ID, treatment sequence, treatment, baseline age, sex, associated AE, first and last dose date for open label Humalog and randomized IP, and the event date.

6.10.4. Hypoglycemic Events and Other Adverse Events

The analysis plans for the following AEs are discussed in Section 6.10.4.1 through Section 6.10.4.5:

- hypoglycemic events
- systemic hypersensitivity reaction
- infusion site reaction
- hepatobiliary events
- malignant neoplasm events

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

6.10.4.1. Hypoglycemic Events

Hypoglycemia events that occur during the study will be captured using a paper diary starting from Visit 2 through Visit 801. Whenever hypoglycemia is suspected, the patient should record the blood glucose value, any associated symptoms, and the treatment administered. A set of events is counted as 1 event in analysis if the duration between adjacent events is ≤30 minutes. The event with the highest severity will be selected for analysis. Severity will be determined in the order of: 1) whether it is a severe hypoglycemia, 2) whether it has symptoms of hypoglycemia reported, and 3) the lowest blood glucose value that occurred. If there are multiple events tied in all 3 aspects, the event with the largest number of nonmissing responses to the questions of nocturnal hypoglycemia and postmeal time frame will be selected. If there are still multiple events tied, the latest event (based on event time) will be selected.

The following types of hypoglycemia events will be derived in the analysis data sets: documented hypoglycemia, severe hypoglycemia, nocturnal hypoglycemia, probable symptomatic hypoglycemia, and overall hypoglycemia. Only severe hypoglycemia will be collected as AEs and all episodes of severe hypoglycemia will be considered as SAEs. Documented hypoglycemia (including documented symptomatic hypoglycemia, documented asymptomatic hypoglycemia, and documented unspecified hypoglycemia) will be based on BG ≤70 mg/dL and BG <54 mg/dL.

Table ITSM.6.4 provides detailed statistical methods for each endpoint related to hypoglycemia. For these analyses, hypoglycemia events from first dose to last dose of IP will be summarized. Additional analyses for other types of hypoglycemic events not mentioned in the table may be conducted as needed.

A listing of patients with at least 1 severe hypoglycemia reported (as SAE) after randomization (including 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 and compared between treatments. Prescott's exact test will be used to assess the treatment difference in the proportion of patients with potential severe hypoglycemia.

Table ITSM.6.4. Summary of Analyses for Endpoints Related to Hypoglycemia

Endpoint	Analysis Period[a]	Statistical Method
Rate of hypoglycemic events (per patient per year) • All Documented[b] • Nocturnal[b] • Non-Nocturnal (or Daytime) (Documented and between waking and bedtime)[b]	0-2, 0-4, 2-4 weeks	Wilcoxon signed-rank test
Incidence of hypoglycemic events • All Documented[b] • Nocturnal[b] • Non-Nocturnal (or Daytime)(Documented and between waking and bedtime)[b]	0-2, 0-4, 2-4 weeks	If there are ≥5 patients with at least one event within the specified time period, a generalized linear mixed model with options of the binomial distribution and logit link function with treatment, period, sequence. The within-patient error will be modeled as a compound symmetry without heterogeneous variance-covariance matrix. If the model does not converge or is not conducted due to the lower occurrence of events, Prescott's exact test will be used for analyses.
Endpoint	**Analysis Period[a]**	**Statistical Method**
Rate of post-meal hypoglycemic events (per patient per year) • Documented[b]	≤1, ≤2, ≤4, >4 and >2 to ≤4 hours after start of a meal within 0-2, 0-4, and 2-4 weeks	Wilcoxon signed-rank test
Incidence of post-meal hypoglycemic events • Documented[b]	≤1, ≤2, ≤4, >4 and >2 to ≤4 hours after start of a meal within 0-2, 0-4, and 2-4 weeks	If there are ≥5 patients with at least one event within the specified time period, a generalized linear mixed model with options of the binomial distribution and logit link function with treatment, period, sequence. The within-patient error will be modeled as a compound symmetry without heterogeneous variance-covariance matrix. If the model does not converge or is not conducted due to the lower occurrence of events, Prescott's exact test will be used for analyses.
Rate of severe hypoglycemic events (per patient per year / 100 years)	0-2, 0-4, 2-4 weeks	Exposure adjusted rate per year / 100 years (calculated for each patient by total number of events divided by total exposure) will be provided and Wilcoxon signed-rank test will be used for treatment comparison.
Incidence of severe hypoglycemic events	0-2, 0-4, 2-4 weeks	Proportion of patients with severe hypoglycemia will be reported. The treatment comparison will be based on Prescott's exact test.

[a] Treatment comparisons for severe hypoglycemia will be based upon the data collected for 0-4 weeks of each treatment period. Treatment comparisons for other categories of hypoglycemia will be only based upon the data collected for 2 to 4 weeks.

[b] Hypoglycemia will be based on the thresholds of blood glucose ≤70 mg/dL and blood glucose <54 mg/dL.

6.10.4.2. Systemic Hypersensitivity Reaction

The number and proportion of patients experiencing treatment-emergent potential systemic hypersensitivity reactions will be summarized and compared by treatment using Prescott's exact test. The following Standardised MedDRA Query (SMQ) will be used to identify potential systemic hypersensitivity reactions from all TEAEs:

- anaphylactic reaction (SMQ). Besides using the narrow and broad terms designated within the SMQ, the following search algorithm will also be implemented as another approach to determine if a patient had an anaphylactic reaction: if a patient (had at least 1 event in Category A) or (had at least 1 event that is in category B and also had at least 1 event that is in category C) or (had at least 1 event that is in category D and [also had at least 1 event in category B or at least 1 event in category C])
- angioedema (SMQ)
- hypersensitivity (SMQ)

Specifically, the following need to be performed: (1) any narrow or algorithmic term from any 1 of the 3 SMQs indicated above (that is, combined search across narrow and algorithmic portions of all 3 SMQs); (2) any narrow scope term within each SMQ, separately (that is, narrow SMQ search); (3) any term within each SMQ, separately (that is, broad SMQ search); (4) narrow scope term search within each SMQ, report the PT nested within each SMQ.

A similar summary will be provided for the TEAE reported by the investigator as possibly related to study drug.

Note that an individual patient may contribute multiple events. Also, a single event may satisfy multiple SMQs, in which case the event contributes to every applicable SMQ.

6.10.4.3. Infusion Site Reaction

The infusion site reactions will be searched by MedDRA PTs from all TEAEs. The number and percentage of patients experiencing at least one treatment-emergent infusion site reaction will be summarized and compared by treatment using Prescott's exact test.

For infusion site reactions identified by MedDRA PTs, the presence and severity of erythema, induration, pain, pruritus, and edema are collected on the eCRF and will be summarized for each treatment. There will be no statistical comparison between treatments.

6.10.4.4. Hepatobiliary Events

6.10.4.4.1. Treatment-Emergent Potential Hepatic Disorder

The percentages of patients with treatment-emergent drug-related hepatic disorder events will be summarized and compared by treatment using MedDRA PT nested within each SMQ, and ordered by decreasing frequency. The following SMQs based on MedDRA will be used to identify potential hepatic disorders:

- broad and narrow terms in the Liver related investigations, signs and symptoms SMQ (20000008)

- broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009)
- broad and narrow terms in the Hepatitis non-infections SMQ (20000010)
- broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)
- narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015)

The percentage of patients with any 1 of the terms will be summarized, in addition to the percentages for each MedDRA PT. The percentages of patients with potentially drug-related hepatic disorders that lead to permanent study discontinuation will be summarized similarly.

6.10.4.5. Malignant Neoplasm Events

The Malignant tumors SMQ will be used to identify treatment-emergent malignant neoplasm event.

6.10.5. Clinical Laboratory Evaluation

The data from safety laboratory measures will be only collected at Visit 1 or Visit 4 for patient safety. Therefore, no by-treatment summary or statistical analysis will be provided.

6.10.6. 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 by week (relative to the start of each randomized treatment period) for patients who have both baseline and at least 1 post-baseline result.

The measurements during the treatment period (0 to 4 weeks during each randomized treatment period) will be analyzed by MMRM model with treatment, baseline value of the response variable, sequence, period, week (defined from the start of each randomized treatment period), and week by treatment interaction as fixed factors and patient as the random factor.

Change from the minimum value during the baseline period to the minimum value during the 2 randomized treatment periods for vital signs and physical characteristics will be summarized by treatment for patients who have both baseline and at least 1 post-baseline result. Baseline will be the minimum of nonmissing observations in the baseline period. The minimum value in the treatment period will be analyzed. Similarly, change from the maximum value during the baseline period to the maximum value during each of the 2 randomized treatment periods (Period I and Period II) for vital signs and physical characteristics will be summarized by treatment for patients who have both baseline and at least 1 post-baseline result. Baseline will be the maximum of nonmissing observations in the baseline period. The maximum value in the treatment period will be analyzed. Planned and unplanned measurements will be included in the analysis.

The percentages of patients with treatment-emergent high or low vital signs and weight at any time after randomization during each of the 2 randomized treatment periods (Period I and Period II) will be summarized and compared between treatments using Prescott's exact test for patients who have both baseline and at least 1 postbaseline measurement. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time that meets the specified change criteria during the 2 randomized treatment periods. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time that meets the specified change criteria during the 2 randomized treatment periods. Table ITSM.6.5 will be used to define the low and high limits and change thresholds.

Table ITSM.6.5. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg) (Consistent clothing and timing in relationship to meals and voiding)	(Loss) decrease ≥7%	(Gain) increase ≥7%

Abbreviations: BP = blood pressure.

6.10.7. Pump-related Safety Analyses

The protocol requires that patients change infusion set every 3 days, unless a change is required for failure of the infusion set in which case an unplanned infusion set change with noted reason needs to be reported in the patient's study diary and transferred to the eCRF. Accordingly, all infusion set changes captured in the CareLink raw data will be classified into 2 categories: planned and unplanned. An infusion set change will be classified as "unplanned" if there is an unplanned infusion set change reported in eCRF linked by time (within a 12-hour window, considering the fact that the patient-reported infusion set change time for eCRF could be slightly off the precise change time stored in the CareLink raw data). Other infusion set changes will be classified as "planned".

If there are unplanned infusion set changes reported in the eCRF that do not have linked records in the Carelink raw data (potentially due to misreporting), these records will be excluded from the calculation of time until infusion set changes and will be reported in the Electronic Trial

Master File (eTMF) as permanent data issues. To be conservative, these infusion set changes will be still included in the analysis of rate and incidence of unplanned infusion set changes.

The incidence (percent of patients with at least 1 event) and rate will be analyzed using Prescott's exact test and Wilcoxon signed-rank test, respectively for planned, unplanned infusion set changes for any reason and for each individual reason (pump occlusion alarm, unexplained high BG, infusion site reaction [pain, redness or swelling at infusion site], infusion set problem [infusion set kinked, pulled out, leaking, reservoir empty, etc.]), by overall (across all infusion set wear days) and by infusion set wear day (Day 1, Day 2,and Day 3).

6.10.7.1. Time until Infusion Set Changes

Date and time of all infusion set changes will be captured in the CareLink raw data. Time interval until infusion set change for each infusion set can be derived based upon the CareLink raw data by calculating the time difference (hours) between the infusion set change and its previous infusion set change.

For each treatment period (lead-in, Period I and Period II), time interval until infusion set change (overall, planned, unplanned, or unplanned due to unexplained high BG) will be derived by averaging across the corresponding infusion set changes that occur within the period. The analyses for time interval (overall and planned) will be then conducted by an MMRM model similar to that for the primary endpoint. Time interval until unplanned infusion set change due to unexplained high BG will be summarized by treatment. No treatment comparison will be conducted due to the low occurrence.

6.10.7.2. Unplanned Infusion Set Changes

A listing of all unplanned infusion set changes will be generated for the Enrolled Population. For each unplanned infusion set change, the following information will be provided:

- the most recent SMBG within 1 hour before the infusion set change measured by the study meter
- the most recent glucose within 1 hour before the infusions set change transferred/entered in the pump
- the 3 most recent CGM values within 20 minutes before the infusion set change
- the reason for the infusion set change
- the infusion set wear day on which the infusion set change occurs
- the infusion set cannula length at screening
- the infusion set cannula length at the time of the infusion set changes

In addition, a listing of unplanned infusion set changes due to unexplained high BG will also be generated. This listing will include the following additional information about the glucose response to the correction boluses, if any, that are delivered as

"CLOSED_LOOP_BG_CORRECTION" within 1 hour prior to the infusion set change, according to the CareLink raw data:

- date and time of the correction bolus
- the most recent SMBG within 1 hour before the correction bolus measured by the study meter
- the most recent glucose within 1 hour before the correction bolus transferred/entered in the pump
- the 3 most recent CGM values within 20 minutes before the correction bolus
- the 3 CGM measures within the time interval of [1 hour -10 minutes, 1 hour +10 minutes] following the correction bolus that were collected prior to the infusion set change
- the most recent SMBG within 1 hour + 10 minutes following the correction bolus measured by the study meter
- the most recent glucose within 1 hour + 10 minutes following the correction bolus transferred/entered in the pump

6.10.7.3. Infusion Set Cannula Length

A listing of infusion set cannula length changes will be generated for the Enrolled Population. For each cannula length change, the following information will be included but not limited to:

- date and time of the change
- cannula length before and after the change
- exposure days to IP of the current study period before and after the change
- number of infusion site reactions (with severity) before and after the change
- number of unplanned infusion set changes due to "Infusion Site Reaction (Pain, Redness or Swelling at Infusion Site)" or due to "Infusion Set Problem (Infusion Set Kinked, Pulled Out, Leaking, Reservoir Empty)" before and after the change

6.10.7.4. Significant Events during Pilot Safety Assessment

For the patients in the pilot safety assessment, the following safety events that occur during the safety assessment period can be identified from the listings of SAE, AE, and unplanned infusion set changes for the study.

- severe hypoglycemia
- DKA
- unplanned infusion set change due to unexplained hyperglycemia (date, time and reason of change)

6.10.8. 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 by treatment sequence for the Randomized Population. The listing of important protocol deviations for the Randomized 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 to last dose of study drug (ie, open-label Humalog used during the lead-in period or IP used during each of the randomized treatment periods [Period I and Period II]), excluding data (if any) that are collected while patients temporarily are off pump or off study treatment.

All of the variables will be derived for the lead-in period, Period I, and Period II. For the lead-in period, the variables will be derived based upon the data collected during the 2-week open-label Humalog treatment period. For Period I and Period II, the variables will be derived for 0 to 2, 2 to 4, and 0 to 4 weeks relative to the start of each randomized treatment period, respectively. Due to the crossover design, treatment comparisons will be based upon the derived outcome variables for 2 to 4 weeks.

Table ITSM.6.6 lists all numerical measures for CGM data, including all primary, secondary and exploratory CGM outcome variables.

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 ITSM.6.6. 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	X
	Duration (in minutes) and percentage of time with sensor glucose values within target range 70 to 140 mg/dL [3.9 and 7.8 mmol/L], both inclusive	X	X	X	X
	Duration (in minutes) and percentage of time with sensor glucose values ≤180 mg/dL [10.0 mmol/L]	X	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: Hyperglycemic Episodes					
	Duration (in minutes) and percentage of time with glucose values >180, 181-250 and >250 mg/dL [10.0, 13.9, and 16.7 mmol/L] and hyperglycemic episodes, defined as at least 10 consecutive minutes >180, 181-250 and >250 mg/dL [10.0, 10.1-13.9 and 13.9 mmol/L]	X	X	X	
	Rate (events/patient/year) and incidence (percent of patients with at least 1 event) of hyperglycemic episodes, defined as at least 10 consecutive minutes >180 and >250 mg/dL [10.0 and 13.9 mmol/L]	X	X	X	

Outcome Measures of CGM Data

Category	Endpoints	24-Hour	Daytime[a]	Nighttime[b]	By Meal[c]
Efficacy Endpoint: Daily CGM Data Summary					
	Area under the curve (AUC)	X	X	X	
	Mean sensor glucose	X	X	X	
	Median sensor glucose	X	X	X	
	Hourly mean sensor glucose	X			
	Hourly median sensor glucose				
Efficacy Endpoint: Glucose Variability and Risk Assessment					
Within-Day	CV	X	X	X	X
	SD	X	X	X	X
	IQR	X	X	X	X
	MAGE	X	X	X	X
	LBGI: frequency and extent of low BG readings	X	X	X	X
	HBGI: frequency and extent of high BG readings	X	X	X	X
	BGRI = LBGI + HBGI: a measure of overall variability and risks of hypo- and hyperglycemia	X	X	X	
Between-Day	CV	X	X	X	
	SD	X	X	X	
	MODD	X	X	X	
Overall[e]	CV	X	X	X	
	SD	X	X	X	
	IQR	X	X	X	
	LBGI	X	X	X	
	HBGI	X	X	X	
	BGRI	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

Outcome Measures of CGM Data

Category	Endpoints	24-Hour	Daytime[a]	Nighttime[b]	By Meal[c]
Safety Endpoint: Hypoglycemic Episodes[f]					
	Duration (in minutes) and percentage of time with sensor glucose values <54, 54-69 and <70 mg/dL of hypoglycemic episodes, defined as at least 10 consecutive minutes <54 and <70 mg/dL [3.0, 3.0-3.8 and 3.9 mmol/L]	X	X	X	X
	Rate (events/patient/year) and incidence (percent of patients with at least 1 event) of hypoglycemic episodes, defined as at least 10 consecutive minutes <54 and <70 mg/dL [3.0 and 3.9 mmol/L]	X	X	X	X
Safety Endpoint: Other					
	Duration (in minutes) of hypoglycemic episode (defined as at least 10 consecutive minutes <54 and <70 mg/dL [3.0 and 3.9 mmol/L])	across all hypoglycemic episodes with duration at least 10 consecutive minutes			
	Duration (in minutes) of each individual hypoglycemic episode (defined as at least 10 consecutive minutes <54 and <70 mg/dL [3.0 and 3.9 mmol/L])	across all hypoglycemic episodes with duration at least 10 consecutive minutes			

Abbreviations: AUC = area under curve; BGRI = blood glucose risk index; CGM = continuous glucose monitoring; CV = coefficient of variation; HBGI = high blood glucose index; hr = hour; IQR = interquartile range; LBGI = low blood glucose index; MAGE = mean amplitude of glycemic excursions; MODD = mean of daily differences; 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). CCI [redacted] 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 (e.g. 2 to 4 weeks relative to the start of each of the randomized treatment period).

[f] In addition, postprandial hypoglycemia episodes 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 (according the CareLink raw data) before the end of time interval.

To assess the glucose control over the course of approximately 3 days of continuous insulin infusion, the duration and percentage of time in ranges (target, hypoglycemia or hyperglycemia) and incremental AUCs after meals, will be derived based upon the CGM raw data collected on each of the infusion set wear days, including Day 1 (>0 and ≤24 hours), Day 2 >24 and ≤48 hours), and Day 3 (>48 and ≤72 hours) and summarized by treatment.

Hypoglycemia/hyperglycemia rates as measured by CGM data will be summarized for 1 year. The rate of hypoglycemia and hyperglycemia will be compared between treatments using Wilcoxon signed-rank test.

The proportion of patients with at least 1 hypoglycemia/hyperglycemia event as measured by CGM data in each category (incidence) during a specific period after randomization will be analyzed using a generalized linear mixed model with options of the binomial distribution and logit link function with treatment, period, and sequence. The within-patient error will be modeled as an unstructured variance-covariance matrix. Prescott's exact test will be conducted as sensitivity analyses. Similarly, the proportion of patients who have achieved the guidance (Battelino 2019) recommended CGM targets of glycemic control (Table ITSM 6.7) during the 2 to 4 weeks of each treatment period will be summarized by treatment and analyzed using the same analysis methods.

Table ITSM 6.7. 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	
<70 mg/dL (3.9 mmol/L)	<4%
<54 mg/dL (3.0 mmol/L)	<1%
hyperglycemia range	
>180 mg/dL (10.0 mmol/L)	<25%
>250 mg/dL (13.9 mmol/L)	<5%

When calculating postprandial-related CGM variables (e.g. time in ranges, within-day variability), any data that are collected after the next meal event will be excluded from analyses for the current meal. Time in ranges by meal will be derived for 0 to 1 hour, 0 to 2 hours, 0 to 3 hours and 0 to 4 hours after the start of each meal while variability by meal will only be derived for 0 to 4 hours. The variability for overall (across meals) will be calculated as the average of the variability from 3 meals.

Other than that, all continuous variables (actual and change from baseline, if applicable) will be compared between LY900014 and Humalog at Week 4 using the MMRMs 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 Weeks 2 to 4 of each randomized treatment 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 weay day (Day 1, Day 2, and Day 3), based upon data from the infusion sets with ≥60 hours of wear.
- 0 to 4 hours relative to meal starting time, by meal (breakfast, lunch, and dinner) and by infusion set wear day (Day 1, Day 2, and Day 3) by pump bolus speed at baseline, including only patients who maintained the pump bolus speed during the lead-in, Period I and Period II, based upon data from the infusion sets with ≥60 hours of wear.

The following individual patient-level plots will be done in R Shiny, including CGM, and all relevant information of SMBG, calibration, infusion set changes dose, carb, or pump settings. Details for these R Shiny plots are provided in a separate document.

- individual level 24-hour for any date
- individual level 24-hour by infusion set wear day for any infusion set: Day 1 (>0 and ≤24 hours); Day 2 >24 and ≤48 hours); Day 3 (>48 and ≤72 hours)
- individual level by meal (overall and by infusion set wear day): breakfast – Day 1 to 3; lunch – Day 1 to 3; dinner – Day 1 to 3

6.14. Subgroup Analyses

The following subgroup will be explored, using the Randomized population, to evaluate consistency of treatment effects on the primary endpoint, if there are at least 10 patients in each subgroup:

- pump bolus delivery speed at baseline (Standard [1.5 U/min], Quick [15 U/min]) including only patients who maintained the pump bolus speed during the lead-in, Period I and Period II
- hemoglobin A1c stratum (≤7.0%, >7.0%)
- percentage of time with SG values from 70 to 180 over the 2 weeks prior to randomization (≤75%, >75%)

The insulin doses will be summarized and analyzed by infusion set wear day (overall, Day 1, Day 2, and dDay 3) and by meal (breakfast, lunch, and dinner), by the subgroup defined using the pump bolus delivery speed at baseline, including only patients who maintained the pump bolus speed during the lead-in, Period I, and Period II. Additional exploratory subgroup analyses may be performed. No tests for treatment by subgroup interaction will be performed.

6.15. 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 treatment, 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

The purpose of this unblinding plan is to maintain the scientific integrity of the study. The following actions/procedures will be put in place prior to any unblinding of the study data.

This is a double-blind study where investigators and patients are not aware of their assigned treatment. Study treatment codes will be scrambled in the analysis data sets until the primary database lock and therefore, there will be no other unblinding for this study.

8. References

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9. Appendices

Appendix 1. Derivation of CGM Variables

9.1. General Derivation Specifications

All CGM variables will be derived for each patient, for each time interval of each study period (lead-in, Period I, and Period II), based upon the data from valid CGM session days (Section 6.13). For Period I and Period II, the variables will be derived for 0 to 2, 2 to 4 , and 0 to 4 weeks relative to the start of each randomized treatment period, respectively.

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 (eg, mean of daily difference [MODD]).

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 pump and on IP, will be included in the derived.

9.2. Glucose in Target Ranges, Hypoglycemia- or Hyperglycemia

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 135 observations with glucose values <70 mg/dL (3.9 mmol/L) out of a total of 3078 observations recorded during the 24-hour period across days for Visit 7, the percentage of time spent in hypoglycemia during the 24-hour period for this patient at Visit 7 will be calculated as 135/3078 = 4.4%. The duration (in minutes) with hypoglycemia (glucose value <70 mg/dL [3.9 mmol/L]) during the 24-hour period for this patient at Visit 7 will be calculated as the percentage times 1440, (ie, 135/3078*1440 = 63.2 minutes).

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. Hypoglycemic/Hyperglycemic Episodes

Hypoglycemic/hyperglycemic episodes as measured by CGM data are defined as at least 10 consecutive minutes below/above the specified threshold, and determined by 3 or more consecutive CGM values meeting the criterion.

The number of distinct hypoglycemic episodes that start will be derived along with days of CGM use (Section 6.13) to calculate the rate of hypoglycemic episodes during a 24-hour period. For example, the rate of postprandial hypoglycemic episodes (<70 mg/dL [3.9 mmol/L]), during the 24-hour period, will be calculated with the following steps:

- Step 1: identify all events as runs of 3 or more consecutive CGM values meeting the criterion, where the pre-marker glucose value (<70 mg/dL[3.9 mmol/L]). Consecutive implies no gaps in time more than 6 minutes between measurements. Events will be identified without regard for the CGM level prior to the start of the meal event.

- Step 2: Count the number of distinct events over the 24-hour period.
- Step 3: Calculate rate per month by multiplying count by 30/days of CGM use. Days of CGM use will be calculated as the number of observations during the 24-hour period divided by the observation supposed to be measured during the period (288 observations for the 24-hour period).

9.6. 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* unless otherwise specified under MAGE definition.

9.6.1. 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):

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

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

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

Mean amplitude of glycemic excursions (MAGE) (Service et al. 1970, 1987; Baghurst 2011): MAGE is the mean of the excursions between consecutive peaks and nadirs in BG that meet qualifying criteria,

$$\mathrm{MAGE}_k = \frac{\sum_{l=1}^{p} \left| \mathrm{BG}_{k,l} - \mathrm{BG}_{k,l-h} \right|}{p}$$

where,

$BG_{k,l}$ = the low point in consecutive BG time points for the k^{th} day (nadir)

$BG_{k,l-h}$ = the high point in consecutive BG time points for the k^{th} day (peak)

p = the number of qualifying excursions: $(BG_{k,l} - BG_{k,l-h}) \geq 1\ SD_k$ and that follow the direction of the first qualifying difference within the BG time points for the *k*th day.

MAGE- and MAGE+ will also be calculated for both negative and positive excursions, in addition to MAGE+/- for all positive and negative excursions combined (Baghurst 2011). The peaks and nadirs will be algorithmically (Baghurst 2011; Approach 1), using a variant that removes the proposed and unnecessary first step of using a smoothing function.

9.6.2. 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):

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

Between-day glucose coefficient of variation (CV):

$$CV = \frac{1}{n}\sum_{i=1}^{n} CV_i = \frac{1}{n}\sum_{i=1}^{n} \frac{\mathrm{SD}_i}{\left(\frac{\sum_{k=1}^{m} \mathrm{BG}_{k,i}}{m} \right)} \times 100$$

Mean of daily differences (MODD): this parameter is calculated as the mean of absolute differences between glucose values at corresponding time points of consecutive days.

$$\mathrm{MODD} = \frac{1}{m-1}\sum_{k=1}^{m-1} \frac{\sum_{i=1}^{n} \left| \mathrm{BG}_{k+1,i} - \mathrm{BG}_{k,i} \right|}{n}$$

9.6.3. Overall Variability

The CV, SD, IQR, low blood glucose index (LBGI), high blood glucose index (HBGI), and blood glucose risk index (BGRI) will be calculated using the standard formulas across collected across all valid days for time interval in each randomized treatment period.

9.6.4. Risk for Hypo/Hyperglycemia

The LBGI has been developed to quantitate both frequency and severity of hypoglycemia. The LBGI has been validated as a predictor of severe hypoglycemia, which is a SAE and could result in coma or death if unrecognized and untreated. The HBGI quantifies both frequency and severity of hyperglycemia and has been related to HbA1c and risk for hyperglycemia (Kovatchev et al. 2005). Additionally, both the LBGI and HBGI have a high sensitivity to changes in glycemic profiles and control (Kovatchev et al. 2005). Low blood glucose index is a non-negative number that increases as the number of low readings increases. High blood glucose index is a non-negative number that increases as the number of high readings increases.

The LBGI, HBGI, and BGRI will be derived for each day of a visit and for overall in the following steps:

Step 1: For each blood glucose (BG [mg/dL]) at the ith time point, compute the following:

$f(BG_i) = 1.509 \times [(\ln(BG_i))^{1.084} - 5.381]$

This transforms the BG data using a nonlinear transformation that maps the BG range of 20 to 600 mg/dL to a symmetric interval of $\left(-\sqrt{10}, \sqrt{10}\right)$

The center of the BG scale is 112.5 mg/dL and is mapped to 0

Step 2: Compute BG risk for each reading

$rl(BG_i) = 10 \times f(BG_i)^2$ if f(BG) < 0; otherwise $rl(BG_i) = 0$

$rh(BG_i) = 10 \times f(BG_i)^2$ if f(BG) > 0; otherwise $rh(BG_i) = 0$

Assign the risk of each BG value by applying the above quadratic risk function

Value range from 0 (achieved when BG = 112.5, the center) to 100

Left side of the parabola is risk of hypoglycemia, and the right side is risk of hyperglycemia

Step 3: Compute LBGI and HBGI

$$LBGI = \frac{1}{n}\sum_{i=1}^{n} rl(BG_i)$$

$$HBGI = \frac{1}{n}\sum_{i=1}^{n} rh(BG_i)$$

Step 4: Compute BGRI

BGRI = LBGI + HBGI

9.7. 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.

9.8. 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).

9.9. Highest Postprandial Glucose

9.9.1. 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.

9.9.2. 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.

9.10. Other

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

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