I8B-MC-ITRO Statistical Analysis Plan Version 2

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog in Adults with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion: PRONTO-Pump-2

NCT03830281

Approval Date: 22-Jan-2020

1. Statistical Analysis Plan: I8B-MC-ITRO: A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog in Adults with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion: PRONTO-Pump-2

LY900014

Study I8B-MC-ITRO is a Phase 3, prospective, randomized, double-blind, outpatient, multi-national, multi-center, 2-treatment group parallel, active-controlled study conducted in patients with type 1 diabetes currently using continuous subcutaneous insulin infusion.

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Protocol I8B-MC-ITRO
Phase 3

Statistical Analysis Plan version 1 electronically signed and approved by Lilly on 24 October 2019
Statistical Analysis Plan version 2 electronically signed and approved by Lilly on date provided below.

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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-ITRO approved on 17 October 2018 and the following amendments (a), (b) and (c) approved on 28 March 2019, 21 June 2019, and 8 October 2019 respectively. This SAP was approved prior to the unblinding of the treatment assignments.

Statistical analysis plan (SAP) Version 2 was approved prior to first unblinding and database lock. The main changes are listed below:

1. For the continuous glucose monitoring (CGM) analyses, clarified the rules for defining data on investigational product (IP), the derivation of CGM endpoints for Visit 10, the analysis method for CGM continuous endpoints, and the minimum percentage of patients in each subgroup to conduct treatment-by-subgroup interaction analyses; added analyses using the intention-to-treat (ITT) estimand for the multiplicity-adjusted endpoints, removed mean amplitude of glycemic excursions (MAGE), low blood glucose index (LBGI) and high blood glucose index (HBGI) from by-meal analyses, as MAGE is not relevant for by-meal analyses and LBGI and HBGI can be assessed alternatively by the other planned analyses (for example, time in range by meal).
2. Added specifications for classification of hypoglycemia events that occur within 30 minutes of each other.
3. Added specifications excluding mixed meal tolerance test (MMTT) infusion set changes from the analysis of time to infusion set change and the exclusion of time intervals >7 days from the analysis due to probable missing data.
4. Added specification for handling duplicate infusion set changes occurring at the same date and time.

4. Study Objectives

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

Table ITRO 4.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
1. To test the hypothesis that LY900014 is noninferior to Humalog on glycemic control ([NIM = 0.4% for HbA1c) in patients with T1D using CSII for 16 weeks	1. Difference between LY900014 and Humalog in change from baseline to Week 16 in HbA1c
Multiplicity Adjusted Objectives	
2. To test the hypothesis that LY900014 is superior to Humalog in controlling 1-hour postprandial glucose (PPG)	2. Difference between LY900014 and Humalog in the 1-hour PPG (serum glucose measured 1 hour after the start of the meal) from a MMTT at Week 16
3. To test the hypothesis that LY900014 is superior to Humalog in controlling 2-hour PPG	3. Difference between LY900014 and Humalog in the 2-hour PPG (serum glucose measured 2 hours after the start of the meal) from a MMTT at Week 16
4. To test the hypothesis that LY900014 is superior to Humalog on improving glycemic control (HbA1c)	4. Difference between LY900014 and Humalog in change from baseline to Week 16 in HbA1c
5. To test the hypothesis that LY900014 is superior to Humalog in the duration of time glucose values within target range 70 to 180 mg/dL (3.9 to 10.0 mmol/L), obtained from CGM use during 24-hour period	5. Duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period, from each 14-day CGM session at Week 16
6. To test the hypothesis that LY900014 is superior to Humalog in the duration of time glucose values within target range 70 to 180 mg/dL (3.9 to 10.0 mmol/L), obtained from CGM use during daytime	6. Duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to daytime (0600 hours to midnight), from each 14-day CGM session at Week 16
Other Secondary Objectives	
7. To compare LY900014 and Humalog with respect to the rate of severe hypoglycemic events	7. Rate (events/ patient/100 years) of severe hypoglycemic events from baseline through Week 16
8. To compare LY900014 and Humalog with respect to the rate and incidence of documented postmeal hypoglycemia	8. Rate (events/patient/year) and incidence (percent of patients with at least 1 event) of documented postmeal hypoglycemia within 1 and 2 hours after the start of the meal from baseline through Week 16
9. To compare LY900014 and Humalog with respect to the rate and incidence of documented hypoglycemia	9. Rate (events/patient/year) and incidence (percentage of patients with events) of documented hypoglycemic events from baseline through Week 16

10. To compare LY900014 and Humalog with respect to 1,5-AG	10. Change from baseline 1,5-AG values at Week 16
11. To compare LY900014 and Humalog with respect to 10-point SMBG profiles	11. Change from baseline 10-point SMBG values at Week 16
12. To compare LY900014 and Humalog with respect to total, basal, and bolus insulin dose	12. Change from baseline in bolus/total insulin dose ratio at Week 16
13. To compare LY900014 and Humalog with respect to the proportion of patients achieving HbA1c targets	13. The proportion of patients with HbA1c <7% and ≤6.5% at Week 16
14. To compare LY900014 and Humalog with respect to the duration of time spent in hypoglycemic glucose ranges, obtained from CGM use	14. Duration (in minutes) and percentage of time with glucose values <54 and <70 mg/dL (3.0 and 3.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes <54 and <70 mg/dL, from each 14-day CGM session at Week 16
15. To compare LY900014 and Humalog with respect to the duration of time spent in hyperglycemic glucose ranges, obtained from CGM use	15. Duration (in minutes) and percentage of time with glucose values >180 and >250 mg/dL (10.0 and 13.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes >180 and >250 mg/dL, from each 14-day CGM session at Week 16
16. To compare LY900014 and Humalog with respect to the incidence and rate of pump occlusion alarms that lead to an unplanned infusion set change	16. Rate (events/patient/30 days) and incidence (percent of patients with at least 1 event) of pump occlusion alarms that lead to an unplanned infusion set change from baseline through Week 16
17. To compare LY900014 and Humalog with respect to the incidence and rate of episodes of unexplained hyperglycemia that lead to an unplanned infusion set change	17. Rate (events/patient/30 days) and incidence (percent of patients with at least 1 event of unexplained hyperglycemia > 300 mg/dL confirmed by SMBG that leads to an unplanned infusion set change from baseline through Week 16
Tertiary/Exploratory	
18. To compare the safety of LY900014 and Humalog	18. Adverse events, vital signs, chemistry, and hematology laboratory measures
19. To compare the incidence of treatment-emergent positive anti-insulin lispro antibodies for LY900014 and Humalog	19. Incidence of treatment emergent anti-insulin lispro antibodies
20. To compare LY900014 and Humalog with respect to quality of life as measured by the EQ-5D-5L	20. Change from baseline in EQ-5D-5L UK-population-based health state index score and EQ-VAS score at Week 16.
21. To compare LY900014 and Humalog with respect to diabetes treatment satisfaction as measured by the ITSQ	21. Change from baseline in ITSQ regimen inconvenience and lifestyle flexibility domain scores at Week 16

22. To compare LY900014 and Humalog with respect to changes in body weight	22. Change in weight (kg) from baseline to Week 16
23. To compare LY900014 and Humalog with respect to the time interval until infusion set change	23. Time interval until infusion set change during the 16-week treatment period
24. To compare LY900014 and Humalog with respect to the factors affecting dosing in pumps	24. Actual and change from baseline in factors affecting dosing in pump (CR, ISF, AIT, and frequency of use of non-normal bolus type [Square Wave or Dual Wave]), during the 16-week treatment period
25. To compare LY900014 and Humalog with respect to the proportion of patients achieving improvement from baseline in HbA1c targets	25. The proportions of patients with shifts in HbA1c to <8% and ≤9%, from baseline to Week 16
26. To compare LY900014 and Humalog with respect to glycemic variability	26. Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 10-point SMBG profiles
27. To compare LY900014 and Humalog with respect to the incremental AUCs after all meals, obtained from CGM use	27. Incremental $AUC_{0\text{-}1\ hour}$ and incremental $AUC_{0\text{-}2\ hour}$ after all meals from each 14-day CGM session at Week 16
28. To compare LY900014 and Humalog with respect to the glucose profiles, obtained from CGM use	28. Average glucose for a 24-hour period from each 14-day CGM session at Week 16
29. To compare LY900014 and Humalog with respect to the glucose variability, obtained from CGM use	29. Interquartile range, CV, LBGI, and HBGI from each 14-day CGM session at Week 16

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; AIT = active insulin time; AUC = area under the curve; CGM = continuous glucose monitoring; CR = carbohydrate ratio; CSII = continuous subcutaneous insulin infusion; CV = coefficient of variation; EQ-5D-5L = EuroQol 5D-5L; EQ-VAS = EQ visual analog scale; HbA1c = hemoglobin A1c; HBGI = high blood glucose index; ISF = insulin sensitivity factor; ITSQ = Insulin Treatment Satisfaction Questionnaire; LBGI = low blood glucose index; MMTT = mixed meal tolerance test; NIM = noninferiority margin; SMBG = self-monitored blood glucose; T1D = type 1 diabetes; UK = United Kingdom.

5. Study Design

5.1. Summary of Study Design

Study I8B-MC-ITRO (ITRO) is a Phase 3, prospective, randomized, outpatient, multinational, multicenter, 2-treatment group, parallel, active-controlled, double-blind study conducted in patients with type 1 diabetes (T1D) currently using continuous subcutaneous insulin infusion (CSII) therapy. Patients will be randomized to receive LY900014 or Humalog as both basal and bolus insulin and will administer bolus doses 0 to 2 minutes prior to meal (pre-meal). The study is designed to demonstrate noninferiority of LY900014 when compared with Humalog in change in HbA1c from baseline to Week 16, when both are used via CSII and bolus doses are given prior to the start of the meal. The study periods include 1-week screening, 2-week lead-in, 16-week treatment, and a 4-week safety follow-up. Figure ITRO 5.1 illustrates the study design.

Patients treated with a rapid-acting insulin analog—insulin lispro, insulin aspart, or insulin glulisine via CSII—will be eligible for inclusion in the trial. All patients will use Humalog during the lead-in period. Those treated with either insulin aspart or insulin glulisine at screening will be transferred to Humalog at Visit 2. At Visit 4, patients will be randomized to either LY900014 or Humalog with bolus doses given immediately prior to each meal. Specific elements of this study design will include collection of 10-point self-monitored blood glucose (BG), blinded CGM sessions, and Mixed Meal Tolerance Testing.

5.2. Determination of Sample Size

Approximately 420 patients will be randomized in order that approximately 368 patients complete the study through the primary endpoint at Week 16.

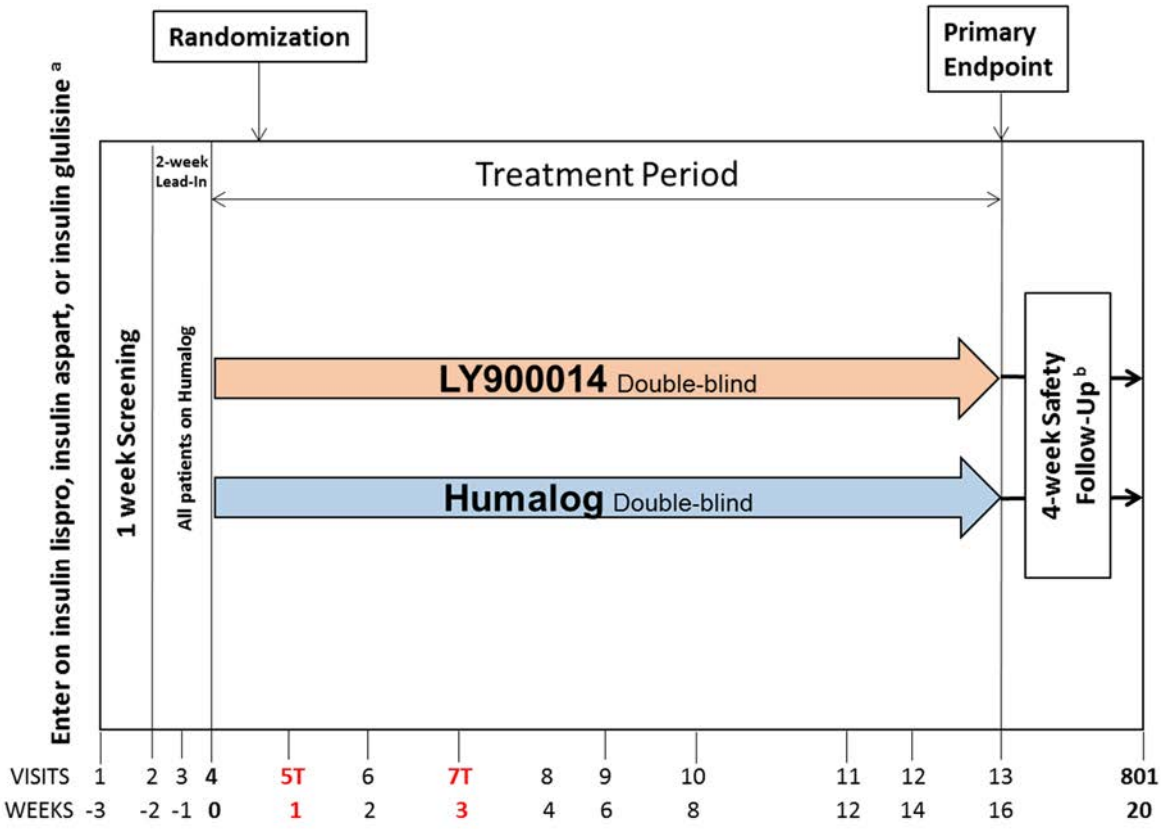
The primary objective of this study is to test the hypothesis that LY900014 is noninferior to Humalog on glycemic control as measured by change from baseline to Week 16 in HbA1c in patients with T1D when administered in a double-blind manner using CSII with bolus doses delivered 0 to 2 minutes prior to the meal.

Patients will be randomized in a 1:1 ratio to double-blind LY900014 with bolus dose delivered 0 to 2 minutes before meals or double-blind Humalog with bolus doses delivered 0 to 2 minutes before meals. Assuming a noninferiority margin (NIM) of 0.4%, no true difference between treatment groups, and a standard deviation (SD) of 0.88%, 368 completers (184 in each treatment group) will provide at least 99% power to show noninferiority between LY900014 and Humalog in change from baseline to Week 16 in HbA1c using the upper limit of a two-sided 95% confidence interval (CI) (LY900014 – Humalog). Assuming a 12% dropout rate for 16 weeks, approximately 420 patients will need to be randomized. This sample size also has 90% power to show noninferiority between LY900014 and Humalog using a 0.3% NIM at Week 16.

5.3. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 4. Assignment to treatment groups will be determined by a computer-generated random

sequence using an interactive web-response system (IWRS). The IWRS will be used to assign all vials containing double-blind IP during the study and open-label Humalog during the lead-in period. Site personnel will confirm that they have located the correct vials by entering a confirmation number found on the vials into the IWRS. Patients will be randomized to 1 of the 2 treatment groups in 1:1 ratio (double-blind LY900014, double-blind Humalog). Stratification will be by country, HbA1c stratum (≤7.5%, >7.5% at Visit 1), and patient's personal CGM or flash glucose monitoring (FGM) use during the study (yes/no). Patients will begin using double-blind IP in their pumps immediately following successful completion of the Visit 4 MMTT. Patients will fill a new pump reservoir and infusion set with IP, then insert a new pump infusion set cannula and begin infusion of IP prior to leaving the investigative site.



Abbreviation: T=Telephone Visits.

[a] Pre-study rapid-acting insulins: insulin lispro, insulin aspart, insulin glulisine via CSII. At Visit 2, patients on insulin glulisine or insulin aspart will be transferred to Humalog. At Visit 4, patients will be randomized to either LY900014 or Humalog.

[b] Patients will discontinue study insulins at Week 16.

Figure ITRO 5.1. Illustration of study design.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter 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 ITRO 6.1.

Table ITRO 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. Treatment group will be defined based on the treatment the patients are assigned.
Safety	All randomized patients who receive at least 1 dose of the randomly assigned IP. Treatment group will be defined based on the treatment the patients were assigned.

Abbreviations: IP = investigational product.

Unless otherwise stated, the efficacy analyses will be conducted on the Randomized Population and the safety analyses will be conducted on the Safety Population.

The primary analysis is for the treatment period up through Week 16.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

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

- Lead-in Period – Visits 2 to 4
- 16-Week Treatment Period – from randomization to Week 16 prior to discontinuation of IP and from randomization to Week 16 (including all data regardless of IP use)
- 16-Week Treatment Period and Safety Follow-Up Visit – from randomization to Visit 801 (including all data regardless of IP use)

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

- For data only measured at an office visit
    - MMTT postbaseline data will be classified as on IP if the MMTT performance date is prior to or on the last IP dose date
    - Other postbaseline data (for example, vital signs, safety laboratory tests, and questionnaires) will be considered as on IP if the measurement was performed at or prior to the cutoff date defined as 14 days after the last IP dose date
- For data collected as running records with an exact date stamp such as adverse events (AEs) and diary entries where the dates of the measures were not tied with the date of an office visit, postbaseline data with dates ≤ (last study drug dose date +1) will be considered as data on IP.
- For CGM data, data collected from first treatment dose date and time to last treatment dose date and time, excluding data collected while patients are temporarily off pump or off IP, will be considered as data on IP.

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

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 actual and the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons.

For laboratory values, both conventional (CN) and System 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.

All baseline measures will be analyzed using an analysis of variance (ANOVA) model that has treatment as the model term.

Table ITRO 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			
TEAEs	All Enrolled Patients	Prior to first dose of open-label insulin lispro (or Visit 2 date if the dose date is missing)	The entire lead-in period after first dose of open-label insulin lispro and prior to the first dose of IP (or Visit 4 date if the dose date is missing).
Basal, bolus, and total insulin doses, and bolus/total insulin dose ratios continuous analysis	All Randomized Patients	Visit 2	Visits 3 to 4 prior to initiation of IP
Pump factors (CR, ISF, AIT)	All Randomized Patients	Visit 2	Visits 3 to 4 prior to initiation of IP
16-Week Treatment Period (including Safety Follow-Up Visit where applicable)			
HbA1c ANCOVA (ITT estimand)	All Randomized Patients with a baseline and at least one post-baseline observation	Last of Visits 1-4	Visit 13 with imputation for patients who discontinue study prior to Visit 13
HbA1c MMRM (efficacy estimand)	All Randomized Patients with a baseline and at least one post-baseline observation while on IP	Last of Visits 1-4	Visits 8, 10, and 13 prior to discontinuation of IP
HbA1c categorical analysis longitudinal logistic regression	All Randomized Patients with a baseline and at least one post-baseline observation while on IP	Last of Visits 1-4	Visits 8, 10, and 13 prior to discontinuation of IP
1-hr and 2-hr PPG and other MMTT variables (ITT estimand)	All Randomized Patients with a post-baseline observation[1]	Visit 4 prior to initiation of IP	Visit 13 regardless of IP use
1-hr and 2-hr PPG and other MMTT variables (efficacy estimand)	All Randomized Patients with a post-baseline observation while on IP[1]	Visit 4 prior to initiation of IP	Visit 13 prior to discontinuation of IP
CGM outcomes	All Randomized Patients with at least one from baseline and post-baseline observations	Visit 4	Visits 10 and 13
Basal, bolus, and total	All Randomized	Last of Visits 2 or 4	Visits 6, 8, 10, and 13 prior to

insulin doses, and bolus/total insulin dose ratios continuous analysis	Patients		discontinuation of IP
Pump factors (CR, ISF, AIT)	All Randomized Patients	Last of Visits 2-4	Visits 6, 8-13 prior to discontinuation of IP
Pump factor: Frequency of each bolus type (normal, square, dual wave) used	All Randomized Patients	Visit 4	Visit 13 prior to discontinuation of IP
10-point SMBG	All Randomized Patients with a baseline and at least one post-baseline observation	Visit 4 prior to initiation of IP	Visits 8 and 13 prior to discontinuation of IP
1,5-AG	All Randomized Patients with a baseline and at least one post-baseline observation	Visit 4 prior to initiation of IP	Visits 8, 10, and 13 prior to discontinuation of IP
Health outcomes: ITSQ, EQ-5D-5L, EQ-VAS	All Randomized Patients with a baseline and a post-baseline observation	Last of Visits 2-4 prior to initiation of IP	Last of Visits 5-13 prior to discontinuation of IP
Safety Laboratory Tests (chemistry, hematology) – continuous analysis	All Patients in the Safety Population with a baseline and a post-baseline observation	Visit 1	Visit 13 (planned) AND last of Visits 5-13 (planned including early discontinuation visits) regardless of IP use
Safety Laboratory Tests (chemistry, hematology) – categorical analysis	All Patients in the Safety Population with a normal baseline (with respect to the direction being analyzed) and a post-baseline observation	Visits 1-4 (including unplanned tests)	Visits 5-13 (including unplanned tests) regardless of IP use
TEAEs	All Patients in the Safety Population	Prior to first dose of randomized IP (or Visit 4 date if the dose date is missing) but after the first dose of open-label insulin lispro in the Lead-in Period	From first dose of randomized IP to last dose of randomized IP AND From first dose of randomized IP to Visit 801
Hypoglycemia events	Safety Population	All Visits 2-4	All Visits 5-13 prior to discontinuation of IP
Unplanned infusion set changes	Safety Population	All Visits 2-4	All Visits 5-13 prior to discontinuation of IP
Weight and vital signs	All Patients in the Safety Population	Last of Visits 2-4	Visits 5-13 prior to discontinuation of IP

	with a baseline and a post-baseline observation		
Anti-insulin lispro antibodies	Safety Population	Visit 4	Visits 5-801 regardless of IP use

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; AIT = active insulin time; ANCOVA = analysis of covariance; CR = carbohydrate ratio; EQ-5D-5L = European Quality of Life – 5 Dimensions 5 Level; EQ-VAS = EuroQol visual analogue scale; HbA1c = hemoglobin A1c; IP = investigational product; ISF = insulin sensitivity factor; ITSQ = Insulin Treatment Satisfaction Questionnaire; ITT = intention-to-treat; LOCF – last-observation-carried forward; MMTT = mixed meal tolerance test; MMRM = mixed-effect model repeated measures; PPG = postprandial glucose; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event.

[1] If the percentage of the patients with missing MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead. See Section 6.11.2.

6.2. Adjustments for Covariates

Stratification factors of this study include country, HbA1c stratum (≤7.5%, >7.5%), and patient's personal CGM or FGM use during the study. Stratification factors will be entered into the IWRS for randomization and also collected in the database by electronic case report form (eCRF) or central laboratory. The analysis models will use the stratification factors as collected at randomization in the database as fixed effects.

For the primary analysis of HbA1c, the stratification factor of HbA1c stratum will not be included. Instead, the continuous value of baseline (Visit 4) HbA1c will be included in the analysis models.

6.3. Handling of Dropouts or Missing Data

The analyses of the primary and multiplicity adjusted objectives will be performed for the ITT estimand and the efficacy estimand. The ITT estimand includes all data collected through Week 16 regardless of IP use and the efficacy estimand includes data collected prior to permanent discontinuation of IP through Week 16. The analyses of the multiplicity adjusted CGM endpoints for the efficacy estimand will also exclude data that are collected while patients are temporarily off pump or off study treatment.

For the Food and Drug Administration (FDA) submission, the ITT estimand will be used and the imputation of missing data for HbA1c will be performed as described in Section 6.11.1.

For the non-FDA submissions, the efficacy estimand will be used. Missing data will be addressed by using a mixed-effect model repeated measures (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. An analysis of covariance (ANCOVA) model will also be used to analyze continuous variables. For the ANCOVA model, unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward (LOCF) approach, using only postbaseline data.

6.4. Multicenter Studies

Countries in similar geographic regions with fewer than 10 patients, based on the all-randomized population, will be pooled to achieve a pooled country of at least 10 patients. All analyses using country in the model will use a pooled country, unless otherwise specified. The final pooling by country and geographic region will be finalized prior to data lock.

6.5. Multiple Comparisons/Multiplicity

A graphical approach for multiple comparisons (Bretz et al. 2011) will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and multiplicity adjusted objectives listed in Section 4. See Section 6.11.2 for the details of graphical testing scheme.

No multiplicity test adjustment will be made for other objectives.

6.6. Patient Disposition

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

Frequency counts and percentages of all randomized patients completing and discontinuing from the study will be presented for each treatment group. Reasons for discontinuation from the study and study treatment will be compared between treatment groups using Fisher's exact test.

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 all entered patients. Reasons for discontinuation from the study during the lead-in period will be summarized for all enrolled patients.

A listing of the primary reason for treatment discontinuation (if applicable) and study discontinuation will be generated for the Randomized Population.

Patient allocation by investigator, grouped by country, will be summarized indicating the number of patients who enter the study, the number of patients who participate in the lead-in period, the number of patients who are randomized to study treatment, and the number of patients who discontinue the study during the 16-Week treatment period.

A listing of the randomization treatment assignment will be generated for all randomized patients.

6.7. Patient Characteristics

A summary table will be generated for patient and diabetes characteristics at study entry using all randomized patients. 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 group (<25, ≥25 to <30, ≥30 kg/m^2), duration of diabetes, duration of CSII use, insulin pump brand and model, infusion set model, the type of rapid-acting insulin at study entry, total daily dose at study entry, patient's personal CGM or

FGM use during the study (each separately and combined as stratification factor), bolus speed, use of low glucose suspend during the study, HbA1c at study entry and baseline, and HbA1c stratum (based on measurement at baseline).

For continuous variables, the following statistics will be provided: mean, SD, minimum, maximum, and median, and treatment groups will be compared using an ANOVA model with a term of treatment. For categorical variables, summary statistics will include sample size, frequency and percentage, and treatment groups will be compared using Fisher's exact test or Pearson's chi-square test. A listing of patient characteristics at study entry will be provided.

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

For all randomized patients, the number and percentage of patients with historical conditions will be summarized by treatment group using Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) nested within system organ class (SOC), and the number and percentage of patients with preexisting conditions will also be summarized by treatment group using MedDRA PT nested within SOC. Historical conditions are conditions that end prior to inform consent and preexisting conditions are conditions that are still ongoing at inform consent. Events will be ordered by decreasing frequency. No statistical comparisons between treatment groups will be performed.

6.8. Treatment Compliance

No analysis for treatment compliance is planned for this study.

6.9. Important Protocol Deviation

Important protocol deviations (IPD) that potentially compromise data integrity or patients' safety will be summarized by treatment group for all randomized patients. The listing of important protocol deviations for all randomized patients during the entire study will be provided in the CSR. The IPDs identified by site monitoring and clinical database will be integrated in the listing. If the IPD is identified by both methods, only the site monitoring IPD will be presented.

6.10. Concomitant and Prior Therapy

Concomitant medication will be summarized and compared between treatment groups using Fisher's exact test for the Randomized Population during the treatment periods (0 to 16 weeks). 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.

A summary of previous diabetes therapies that were discontinued prior to informed consent will be generated for the Enrolled Population.

The daily basal dose, daily bolus dose, total insulin dose, and the ratio of bolus dose to total insulin dose during the lead-in period will be summarized by visit for each treatment. The doses

and bolus/total insulin dose ratios for each visit will be calculated as the mean of the doses for the last 3 days prior to the visit date that are entered in the eCRF. Doses will be summarized in U and U/kg.

6.11. Efficacy Analyses

6.11.1. Analysis of Primary Objective

The primary objective of this study is to test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (NIM = 0.4% for HbA1c) in patients with T1D using CSII with bolus doses delivered 0 to 2 minutes prior to the meal for 16 weeks. There will be 2 primary analysis methods, each tested at the full significance level of 0.05.

For the United States (US) FDA submission, the primary analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand that will include all data collected from randomization through Week 16, regardless of IP use. The reference will be all observed data from the randomized patients in the same treatment group who discontinue IP and complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog from an ANCOVA model. The model for the change from baseline to the Week 16 HbA1c endpoint will include treatment and strata (country and patient's personal CGM or FGM use during the study) as fixed effects and baseline HbA1c as a covariate.

If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis such that the model cannot converge, or the number of records without missing data is less than the number of records with missing data, the missing HbA1c measurement at Week 16 will be imputed by the patient-level observed baseline value plus a noise, assuming a washout of any potential treatment effect (or "return to baseline"). The noise follows a normal distribution with the variability estimated from the "washout HbA1c data." The "washout HbA1c data" will be derived by subtracting the corresponding treatment mean at Week 16 from individual non-missing HbA1c values at Week 16.

For non-FDA submissions, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog at Week 16 (Visit 13) from the MMRM analysis of change from baseline in HbA1c including data collected from all randomized patients prior to permanent discontinuation of IP through Week 16 (efficacy estimand). The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment, strata (country and patient's personal CGM or FGM use during the study), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on LS means and Type III tests. 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.

For both primary analysis approaches, LY900014 will be declared noninferior to Humalog if the upper limit of the 2-sided 95% CI for the LS mean difference in the change from baseline in HbA1c for LY900014 minus Humalog is below +0.4%. In addition, the 95% CI for the treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05.

In addition to the primary objective, the superiority of LY900014 in controlling HbA1c compared with Humalog will also be assessed for each analysis approach described above. If the p-value is less than the alpha level from the graphical approach allocated to the superiority hypothesis, LY900014 will be declared superior to Humalog.

6.11.2. Analyses of Multiplicity Adjusted Objectives

A graphical approach for multiple comparisons will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary objective (H1) and the following multiplicity adjusted objectives: superiority of LY900014 compared with Humalog for (H2) 1-hour postprandial glucose (PPG) during MMTT at Week 16, (H3) 2-hour PPG during MMTT at Week 16, (H4) change from baseline to Week 16 in HbA1c, (H5) duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period at Week 16, and (H6) duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to daytime (0600 hours to midnight) at Week 16. Analyses will be performed for both the efficacy estimand and ITT estimand.

The graphical testing scheme is displayed in Figure ITRO 6.1. The study total alpha level (or study-wise type I error) is preset to be 5% for each estimand. All the hypotheses are connected by lines with arrowheads indicating the directions of testing paths. The initial allocation of study total alpha for each hypothesis is located within the same node of the hypothesis. The study total alpha level will be used for the primary objective in the initial step. The alpha level will be allocated to other key endpoints based on the weights in testing paths once the primary endpoint is successfully demonstrated. If 1 of the remaining hypotheses is successfully demonstrated with the preserved alpha level, its preserved alpha will be allocated to the remainder of the hypotheses by the weights in the paths. The iterative test procedure continues until none of the remaining hypotheses can be demonstrated with their preserved alphas or all hypotheses are demonstrated successful.

An ANCOVA model with strata (country, HbA1c stratum (≤7.5%, >7.5%), and patient's personal CGM or FGM use during the study) and treatment as fixed effects and baseline as a covariate will be used to analyze the 1-hour and 2-hour PPG for both the efficacy (data collected prior to discontinuation of IP) and ITT (all data collected regardless of IP use) estimands. However, if the percentage of the patients with missing MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead.

Duration with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to 24-hour period and to daytime will be analyzed using a similar MMRM model as used for the primary endpoint.

The superiority testing on change from baseline to the study primary endpoint in HbA1c will be assessed by the same analysis used for the primary objective. The analyses for the ITT and efficacy estimands are described in Section 6.11.1. If the p-value is less than the alpha level allocated by the graphical approach, the superiority of LY900014 to insulin lispro will be achieved.

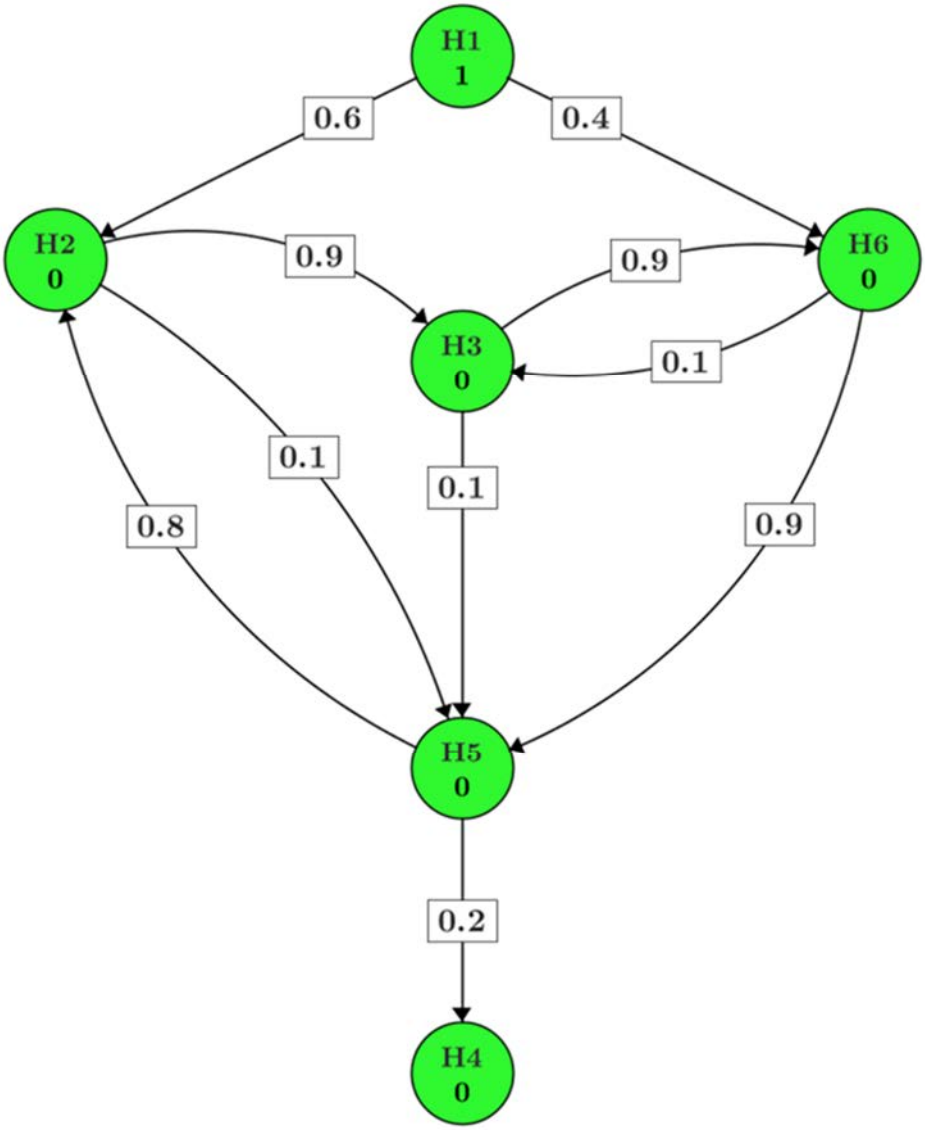


Figure ITRO 6.1. Testing scheme for primary and multiplicity adjusted objectives.

6.11.3. Sensitivity Analyses for Missing Data

A missing-not-at-random-based analysis will be performed for both the efficacy and ITT estimands to assess sensitivity to departures from the missing-at-random (MAR) assumption. The tipping-point approach that will be used is similar to a progressive stress test (Ratitch et al. 2013). The basic idea is to impute the missing values and add a value (delta) to the imputed values of the experimental treatment group and perform an analysis for the primary endpoint on the delta-adjusted data set to see whether the conclusion of the primary analysis is overturned. If not, a larger delta is chosen and the process repeated until the primary result is overturned. If the delta required to overturn the primary result is not a plausible departure from MAR, then the primary result is robust to plausible departures from MAR. The initial delta is set to 0.1 with an

increment of 0.1. Imputation under the noninferiority null method (where delta equals the NIM) will be included as a special case of the progressive stress test.

For the ITT estimand, the reference group will be as described for the FDA primary analysis, and ANCOVA on the change from baseline to Week 16 in HbA1c will be used.

For the efficacy estimand, the reference group will be the Humalog treatment group. Imputation will be for all longitudinal visits.

6.11.4. Other Secondary Efficacy Analyses

The analyses described below will include data collected from all randomized patients prior to permanent discontinuation of IP. The longitudinal observations of actual and change from baseline in HbA1c up to Week 16 will be analyzed using the same MMRM model as for the analysis of the primary outcome. For the following secondary efficacy endpoints, an MMRM model with fixed class effects of treatment, strata (pooled country, HbA1c stratum (≤7.5%, >7.5%) and patient's personal CGM or FGM use during the study), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value.

- actual and change from baseline 1,5-Anhydroglucitol (AG) values
- actual and change from baseline 10-point self-monitored blood glucose (SMBG) values (fasting, 1 hour post morning meal, 2 hours post morning meal, pre midday meal, 1 hour post midday meal, 2 hours post midday meal, pre evening meal, 1 hour post evening meal, 2 hours post evening meal, and bedtime)
- actual and change from baseline in total, basal, and bolus insulin doses and bolus/total insulin dose ratios
- actual and change from baseline in CGM derived time in hypoglycemia and time in hyperglycemia, defined in Section 6.13.

Three 10-point SMBG profiles are expected to be collected during the 2 weeks prior to Visits 4, 8, and 13. Valid SMBG profiles will be used for analysis, defined as having non-missing values at ≥6 time points per day among the 10 pre-specified time points and being collected during 2 weeks prior to a given visit. For each time point, the average of the corresponding SMBG values from the valid SMBG profiles will be used for analysis. The SMBG and the excursion for each meal category (that is, morning meal, midday meal, and evening meal) calculated using the average values at the corresponding time points will be used for analysis.

The basal, bolus, total doses and bolus/total insulin dose ratios for each visit 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.

Derivation and analysis of CGM endpoints are described in Section 6.13.

The following endpoints, collected from the MMTT, will be analyzed using the ANCOVA model with strata (pooled country, HbA1c stratum (≤7.5%, >7.5%), and patient's personal CGM or FGM use during the study) and treatment as fixed effects and baseline as a covariate:

- actual and change from baseline in fasting glucose (average of measurements at time -15 and 0), and PPG at 15, 30, 60, 120, 180, and 240 minutes after the meal
- PPG excursions at time 15, 30, 180, and 240 minutes after the meal (PPG minus fasting glucose)

Sensitivity analysis for PPG and excursions may be performed to exclude patients whose PPG and excursion could be affected by factors including MMTT consumption amount (for example, partial MMTT was consumed).

Treatment comparisons for the proportion of patients with HbA1c <7.0% and ≤6.5% will be analyzed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c-by-visit interaction, and treatment-by-visit interaction. An unstructured covariance structure will be used.

6.11.5. Analyses of Exploratory Efficacy and Health Outcomes Objectives

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 pump factors including carbohydrate ratio (CR), active insulin time (AIT), and insulin sensitivity factor (ISF) will be captured in eCRF throughout the study. A listing of pump factors will be provided including data collected at Visit 2 and the changes captured. Actual and change from baseline in these pump factors will be summarized between LY900014 and Humalog using an MMRM model as specified in Section 6.11. The frequency of bolus type (normal, square or dual wave) used will be collected at Visit 4 and Visit 13 as another pump factor. The frequency of use of non-normal bolus type (square or dual wave), will be summarized and compared between LY900014 and Humalog using an ANCOVA model specified in Section 6.11.

For the Insulin Treatment Satisfaction Questionnaire (ITSQ), the change from baseline to LOCF endpoint while on treatment in each domain transformed score (inconvenience, lifestyle, hypoglycemic control, glycemic control, delivery system) and overall transformed score will be analyzed using the ANCOVA model with strata (pooled country, HbA1c stratum (≤7.5%, >7.5%), and patient's personal CGM or FGM use during the study), and treatment as fixed effects and baseline as a covariate.

Summary statistics, including number of patients and proportion of categorical outcomes (5 levels) for the 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) of the European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L) will be provided by visit and by treatment. The change from baseline to LOCF endpoint (Week 16, Visit 13) in the EQ-5D-5L United Kingdom (UK) population-based health state index score and

EuroQol visual analog scale (EQ-VAS) score will be analyzed using the ANCOVA model with terms same as those for ITSQ analysis.

The proportions of patients with HbA1c <8%, ≤8%, <9% and ≤9% at baseline, Week 16 and LOCF endpoint will be summarized by treatment.

Within-day and between-day glycemic variability measured by the SD and the coefficient of variation (CV) of 10-point SMBG profiles will also be analyzed by the MMRM model specified in Section 6.11.4. At a given visit, the CV and SD on each day with a valid SMBG profile will be calculated using all the glucose values within that day, then the average values of these CVs and SDs will be used as the within-day CV and SD at that visit in analysis. At a given visit, the CV and SD at each of the 10 pre-specified SMBG time points will be calculated using the corresponding glucose values of the valid SMBG profiles, then the average values of these CVs and SDs will be used as the between-day CV and SD at that visit in analysis.

The 1-hour and 2-hour PPG excursions by 10-point SMBG profile and daily average of the 10-point SMBG profile will be analyzed similarly.

The following additional variables from the MMTT will be analyzed using the ANCOVA model described in Section 6.11.2:

- Incremental areas under the serum glucose concentration-time curve (iAUC) from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after the meal in MMTT. iAUC is the total area under the serum glucose curve but above the glucose level at time 0 (average of measurements at time -15 and 0) when the meal starts for the MMTT within the specific time frame. The area will be calculated by trapezoids rule.
- Area under/above the serum glucose concentration time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after the meal in MMTT.
    - AUC: Total area under the serum glucose curve calculated by trapezoids area within the specific time frame
    - AUC>180: Total area under the serum glucose curve but above the 180 mg/dL level within the specific time frame
    - AUC≤70: Total area above the serum glucose curve but below the 70 mg/dL level within the specific time frame.
- Glucose variability during MMTT (CV and SD of all serum glucose values collected during the MMTT).

The incidence of patients with HbA1c <7.0% and ≤6.5% at Week 16 (Visit 13), imputed using LOCF, and no severe hypoglycemia during 16 weeks of treatment will be compared using a logistic regression model with terms for treatment and baseline HbA1c value.

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

6.12. Safety Analyses

Safety measures will include AEs, hypoglycemia, unplanned infusion set changes and reasons, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro.

Continuous safety variables, as well as the change from baseline for these variables, will be analyzed either by MMRM or ANCOVA models. For categorical variables, Fisher's exact test or Pearson's chi-square test will be used to compare treatment groups unless otherwise specified.

6.12.1. 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: <4 weeks (>0 and <28 days), ≥4 and <8 weeks (≥28 and <56 days), ≥8 and <12 weeks (≥56 and <84 days), ≥12 and <16 weeks (≥84 and <112 days) and ≥16 weeks (≥112 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 prematurely are encouraged to remain in the study without study drug. The days on study after discontinuing IP, and the days on study from date of first study drug to the last study visit date up to Visit 801 will also be summarized.

6.12.2. Adverse Events

Events that are newly reported after the first dose of IP or reported to worsen in severity from baseline will be considered treatment-emergent adverse events (TEAEs). 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 by this study, the case report form (CRF)-collected flag will be used to determine whether the event started or worsened post-treatment.

Serious adverse events (SAEs), AEs reported as reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the MedDRA PT, sorted by decreasing frequency within the LY900014 treatment group. Treatment-emergent adverse events will also be summarized by PT sorted by decreasing frequency within SOC for all TEAEs and by maximum severity. For events that are specific to only one sex, the denominator and computation of the percentage will include only patients from the given sex. The number and proportion of patients with at least 1 event for each type of event will be summarized and compared between treatment groups using Fisher's exact test. Serious adverse events, AEs reported as reason for discontinuation from the study, and TEAEs will also be summarized for open-label Humalog during the lead-in period.

6.12.3. Hypoglycemic Events and Other Adverse Events

6.12.3.1. 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 (BG ≤ 70 mg/dL [3.9 mmol/L]), the patient should record the BG 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 with severity determined in the order of: 1) it is a severe hypoglycemia, 2) it has symptoms of hypoglycemia reported, and 3) it has the lowest blood glucose value. If there are multiple events tied in all 3 aspects, the event with the largest number of non-missing responses to the questions of nocturnal hypoglycemia and postmeal time frame will be selected. Hypoglycemia rates will be summarized for periods of 1 year and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical method (see Appendix 1 for details). For each of other categories of hypoglycemia, the number of hypoglycemia events during 0 to 16 weeks (rate) after randomization will be analyzed by using a negative binomial regression model including treatment. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days will be included in the model to estimate the rate of hypoglycemia per year. The proportion of patients with at least 1 hypoglycemic event in each category (incidence) during 0 to 16 weeks after randomization will be analyzed using a logistic regression model including treatment.

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

Table ITRO 6.3 provides detailed statistical methods for each endpoint related to hypoglycemia. For these analyses, hypoglycemia events prior to the discontinuation (i.e., 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. Fisher's exact test will be used to assess the treatment difference in the proportion of patients with potential severe hypoglycemia.

Table ITRO 6.3. Summary of Analyses for Endpoints Related to Hypoglycemia

Endpoint	Analysis Period[b]	Statistical Method
Rate of hypoglycemic events (per patient per year) • All Documented[a] • Nocturnal[a] • Non-Nocturnal (or Daytime) (Documented and between waking and bedtime)[a]	0-16 weeks	Negative binomial regression with treatment and log (exposure/365.25 days) as the offset in the model.
Incidence of hypoglycemic events • All Documented[a] • Nocturnal[a] • Non-Nocturnal (or Daytime) (Documented and between waking and bedtime)[a]	0-16 weeks	Logistic regression with treatment
Rate of post-meal hypoglycemic events (per patient per year) • All Documented[a]	≤1, ≤2, ≤4, and >2 to ≤4, and >4 hours after start of a meal within 0-16 weeks	Negative binomial regression with treatment and log (exposure/365.25 days) as the offset in the model.
Incidence of post-meal hypoglycemic events • All Documented[a]	≤1, ≤2, ≤4, and >2 to ≤4, and >4 hours after start of a meal within 0-16 weeks	Logistic regression with treatment
Rate of severe hypoglycemic events (per patient per 100 years)	0-16 weeks	Exposure adjusted rate per 100 years (calculated by total number of events divided by total exposure for individual patients) will be provided and the empirical method (see Appendix 1 for details) will be used for treatment comparison.
Incidence of severe hypoglycemic events	0-16 weeks	The treatment comparison will be based on a logistic regression model with treatment as a covariate.

[a] All documented hypoglycemia and the subcategories based on the thresholds of BG ≤70 mg/dL and BG <54 mg/dL will be analyzed.

6.12.3.2. Systemic Hypersensitivity Reaction

The number and proportion of patients experiencing treatment-emergent potential systemic hypersensitivity reactions will be summarized and compared by treatment group using Fisher's exact test. The following MedDRA Standardised MedDRA Queries (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, need to perform the following: (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 related to study drug judged by investigator.

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.

6.12.3.3. Infusion Site Reaction

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

For infusion site reactions identified by MedDRA PTs, the presence and severity of erythema, induration, pain, pruritus and edema (collected on the eCRF Infusion Site Reaction Questionnaire form) will be summarized for each treatment. Also, by anatomical location of the reaction for overall infusion site reaction will be summarized. There will be no statistical comparison between treatments.

6.12.3.4. Hepatobiliary Events

6.12.3.4.1. Treatment-Emergent Potential Hepatic Disorder

The percentages of patients with treatment-emergent drug-related hepatic disorder events will be summarized and compared by treatment group using MedDRA PT nested within each SMQ 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 led to permanent study treatment discontinuation will be summarized similarly.

6.12.3.4.2. Liver Enzyme Lab Values

The liver enzyme measures (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], direct bilirubin, total bilirubin) will be summarized by treatment group. Post-baseline value and the change from baseline (last nonmissing value before randomization) to post-baseline value at Week 16 visit (planned test) will be summarized for patients who have both a baseline and at least 1 postbaseline result, and compared between treatment groups by using ANCOVA model with the term of treatment and baseline value of the response variable. All analyses will be provided in both SI and CN units.

The last nonmissing observation at or prior to Week 26 (including early discontinuation visits) will also be analyzed by an ANCOVA model with the term of treatment, baseline value of response variable.

6.12.3.4.3. Treatment-Emergent Elevation of Liver Enzyme Lab Values

The percentages of patients with the following elevations in hepatic laboratory tests at any time during the treatment period (0 to 16 weeks) will be summarized between treatment groups:

- The percentages of patients with post-baseline ALT measurement ≥3 times (3X), 5 times (5X), and 10 times (10X) the Covance upper limit of normal (ULN) will be summarized for all patients with a post-baseline value by the following baseline categories: ≤1X, >1X to <3X, ≥3X, missing.
- The percentages of patients with post-baseline AST measurement greater than or equal to 3 3X, 5X, and 10X the Covance ULN will be summarized for all patients with a post-baseline value by the following baseline categories: ≤1X, >1X to <3X, ≥3X, missing.
- The percentages of patients with post-baseline total bilirubin measurement ≥2 times (2X) the Covance ULN will be summarized for all patients with a post-baseline value by the following baseline categories: ≤1X, >1X to <2X, ≥2X, missing.

Baseline will be the maximum observation in the baseline period including the lead-in period. The maximum value will be the maximum value from the treatment period. Planned and unplanned tests will be included.

Graphical profiles of ALT, AST, total bilirubin, and ALP will be provided for patients with an ALT or AST ≥3X ULN or total bilirubin ≥2X ULN during the treatment period. A listing for these patients will also be provided, including the actual measurement of ALT, AST, ALP, and total bilirubin, the corresponding reference high limits, demographics, disposition, drug exposure and AEs. The review for these patients includes an assessment of the proximity of any ALT or AST elevation to any total bilirubin elevation, ALP levels, other potential causes, and the temporal association with events such as nausea, vomiting, anorexia, abdominal pain, or fatigue.

All patient data, regardless of whether on IP, will be used for the above analyses related to hepatobiliary events.

6.12.4. Clinical Laboratory Evaluation

The data from safety laboratory measures will be summarized at Week 16 where the lab test is planned to be collected. Postbaseline and change from baseline to postbaseline for laboratory tests will be summarized for patients who have both baseline and at least 1 post-baseline result and compared between treatment groups by using ANCOVA model with the term of treatment and baseline value of the response variable. Analyses will be provided in both SI and CN units.

The last nonmissing observation at or prior to Week 16 (planned tests including early termination) will also be analyzed by an ANCOVA model with the term of treatment, baseline value of the response variable.

The percentages of patients with treatment-emergent abnormal, high, or low laboratory results at any time during the treatment period (0 to 16 weeks) will be summarized for patients who have both baseline and at least 1 post-baseline result and compared between treatment groups using Fisher's exact tests. A treatment-emergent abnormal result is defined as a change from normal at all baseline visits to abnormal at any time during the treatment period. 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 during the treatment period. 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 during the treatment period. Planned and unplanned measurements will be included. Covance reference ranges will generally be used to define the low and high limits. Only patients who have normal baseline values for the analysis being performed will be included in the analysis for treatment-emergence.

Liver enzymes measures will not be included in the above analyses as different analyses will be used as described in Section 6.12.3.4.2 and Section 6.12.3.4.3.

6.12.5. Vital Signs and Other Physical Findings

Post-baseline measurements and change from baseline to post-baseline for vital signs and physical characteristics (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, 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 (0 to 16 weeks) will be analyzed by an MMRM model with treatment, baseline value of the response variable, visit, and visit by treatment interaction as fixed factors and patient as the random factor.

An ANCOVA model will also be used for the analysis of the last nonmissing observation (including early discontinuation visit) during the treatment period and during the entire study (up to Visit 801). The ANCOVA models are the same as those used for clinical laboratory measures.

The percentages of patients with treatment-emergent high or low vital signs and weight at any time during the treatment period (0 to 16 weeks) or during the entire study including safety

follow-up period will be summarized by treatment group 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 treatment period or during the entire study including safety follow-up period. 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 treatment period or during the entire study including safety follow-up period. Treatment comparison will be based on Fisher's exact test. Table ITRO 6.4 will be used to define the low and high limits and change thresholds.

Table ITRO 6.4. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight 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.

6.12.6. Pump-related Safety Analyses

6.12.6.1. Time Until Infusion Set Changes

Date and time of all infusion set changes will be captured in the eCRF. Time interval in hours until infusion set change for each infusion set can be derived through a time-to-day conversion by dividing the time difference between the infusion set change and its previous infusion set change by 86400 seconds.

The protocol requires the patients to change infusion set every 3 days unless a change is required for failure of the infusion set. The eCRF captures both the planned and unplanned infusion set changes. For unplanned infusion set changes, BG, the reason for change and ketone test result (when SMBG > 300 mg/dL) will also be captured.

For the entire study period (including lead-in), time to infusion set changes in hours for overall, planned and unplanned infusion set changes will be derived and analyzed. Infusion set changes at MMTT will be excluded in calculating time until infusion set changes, because this change is

a study procedure and does not reflect the patients' behavior. The average time to infusion set change, measured in days, for the following time intervals: (-2)- to 0, 0 to 4, 4 to 8, and 8 to 16 weeks, mapped to Weeks 0, 4, 8, and 16, respectively, will be analyzed using an MMRM model similar to the model used for the primary endpoint. The average time to infusion set change across the entire 0 to 16 weeks will be analyzed using an ANCOVA model.

6.12.6.2. Infusion Set Changes

To handle potential missing input in paper diary for the infusion set changes, time intervals until infusion set change that are greater than 7 days (168 hours) will be excluded from the analysis. If 2 planned infusion set changes happened on the same day at the same time, only 1 will be used for analysis. The same rule applies when there are duplicate unplanned infusion set changes.

The incidence (percent of patients with at least 1 event) and rate for overall, planned and unplanned infusion set changes will be analyzed using Fisher's exact test and Wilcoxon signed-rank test respectively. The unplanned infusion set changes will be analyzed 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.). The unplanned infusion set changes will also be summarized by infusion set wear day (Day1 = ≤24 hours, Day2 = >24 and ≤48 hours, Day3 = >48 and ≤72 hours and Day3+ = >72 hours) by treatment and treatment comparison will only be conducted when there are sufficient number of patients in each treatment arm. 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:

- Cannula length at study entry
- Cannula length at the time of the infusion set change
- BG at time of infusion set change
- the reason for the infusion set change
- the infusion set wear day on which the infusion set change occurs
- the ketone test value associated with the infusion set change when SMBG > 300 mg/dL

A table will be generated to summarize number of patients who have at least 1 unplanned infusion set change due to unexplained high BG with BG (SMBG) > 250 mg/dL (13.9 mmol/L) and with BG (SMBG) > 300 mg/dL (16.7 mmol/L).

6.12.6.3. Infusion Set Model and Cannula Length

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

- Date and time of the change
- Infusion set model before and after the change
- Cannula length before and after the change
- Exposure days to IP 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

A summary table of infusion model/cannula length, number of infusion site reaction, and number of unplanned infusion set changes will be generated by treatment before and after infusion set model and/or cannula length change.

6.12.7. Immunogenicity

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro for all enrolled patients since Visit 4 prior to the first dose of study-provided prandial insulin treatment. Therefore, the blood sample result at Visit 4 will be considered as the anti-insulin lispro level at baseline for this study. The assessment of immunogenicity will include analyses of treatment-emergent anti-insulin lispro antibody up to Visit 801.

6.12.7.1. Treatment Emergent Anti-Insulin Lispro Antibody

The treatment-emergent anti-insulin lispro antibody (denoted as treatment-emergent antidrug antibody [TEADA] throughout this SAP) is based on the change from baseline (Visit 4) to post-baseline (post-Visit 4) in the anti-insulin lispro antibody level (percent binding). Treatment-emergent antidrug antibody can be sub-classified as either treatment-induced (not detected anti-insulin lispro antibody at baseline) or treatment-boosted (detected anti-insulin antibody at baseline):

- treatment-induced response: change from not detected anti-insulin lispro at baseline (Visit 4) to post-baseline detected anti-insulin lispro;
- treatment-boosted response: change from detected anti-insulin lispro at baseline (Visit 4) to post-baseline detected anti-insulin lispro antibody level (percent binding) at least 157% of the baseline value.

The TEADA status during the analysis period will be determined using all data in the corresponding analysis period regardless of IP use. The summary for TEADA status and the anti-insulin lispro antibody level will use the same analysis data.

The number and percentage of patients with positive TEADA response at Visit 4, Visit 13 and Visit 801 will be summarized by treatment group. For patients with positive TEADA response, the number and percentage of patients with positive insulin cross-reactivity will also be summarized by treatment group. Treatment groups will be compared by Fisher's exact test.

Both actual and change from baseline (Visit 4) for the anti-insulin lispro antibody level in percent binding will be summarized by scheduled visit prespecified in the protocol for patients with positive TEADA response from Visit 4 to Visit 801. The repeated measurement from Visit 4 to Visit 801 will be analyzed by an MMRM model with treatment, baseline value of the response variable, visit, and visit by treatment interaction as fixed factors and patient as the random factor. The ANCOVA model using treatment and baseline value as covariates will be

used for the analysis of last non-missing observation prior to or at Visit 801 and the analysis of maximum percent binding during the analysis period of Visit 4 to Visit 801.

A listing of anti-insulin lispro antibody at each visit will be provided. The listing will include anti-insulin lispro antibody status (detected/not detected), anti-insulin lispro antibody percent binding, TEADA status (positive/negative), insulin cross-reactivity status, and insulin cross-reactivity percent binding for the safety population.

Subgroup analysis for the following selected efficacy and safety variables will be performed by the TEADA status during the analysis period of Visit 4 to Visit 801:

- HbA1c and change from baseline in HbA1c
- 1-hour and 2-hour PPG
- basal, prandial, and total insulin dose
- treatment-emergent infusion site reaction and hypersensitivity reaction
- event rate of all documented hypoglycemic events

The analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model for the primary analysis and the HbA1c data prior to permanent discontinuation of IP. The model will include additional fixed terms of subgroup, subgroup by treatment interaction, subgroup by visit interaction, and 3-way interaction of treatment, subgroup and visit.

The PPG will be analyzed by the ANCOVA model same as the model specified in Section 6.11.2 using the efficacy estimand. The model will include additional terms of subgroup, subgroup by treatment interaction, subgroup by visit interaction, and 3-way interaction of treatment, subgroup and visit.

The subgroup analysis for insulin dose will use the MMRM model specified in Section 6.11.4 using the efficacy estimand. The model will include additional fixed terms of subgroup, subgroup by treatment interaction, subgroup by visit interaction, and 3-way interaction of treatment, subgroup and visit.

The treatment-emergent infusion site reaction and hypersensitivity reaction will be analyzed by a logistic regression model including terms of treatment, subgroup, treatment by subgroup interaction. All data regardless of IP use will be used for this analysis.

The negative binomial regression model with treatment with additional terms of subgroup, treatment by subgroup interaction will be used for the subgroup analysis of all documented hypoglycemia event rate while on IP.

The interaction effects (3-way for MMRM and 2-way for ANCOVA/logistic regression model/negative binomial regression model) will be evaluated using a significance level of 0.10, unadjusted. If the interaction effect is significant ($p<0.10$), separate analysis without the terms related with the subgroup will be performed for each subpopulation.

6.12.8. 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:

- 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.

6.13. CGM Analyses

The analyses described in this section will be based on the efficacy estimand, including data collected from first dose to last dose of study drug (i.e., open-label Humalog used during the lead-in period or IP used during the treatment period, excluding data (if any) that are collected while patients are temporarily off pump or off study treatment.

In addition, for the FDA submission, the analyses of the multiplicity adjusted objectives on CGM endpoints will also be performed for the ITT estimand. All of the variables will be derived for baseline, Visit 10 (Week 6-8), and Visit 13 (Week 14-16). For baseline, the variables will be derived based upon the data collected during the 2-week open-label Humalog treatment period. For Visit 10, the derivation will be based upon all the data collected during the visit interval of Visit 9, 10, and 11, taking into consideration that some patients may have the sensor inserted before Visit 9 or have the sensor removed after Visit 10.

Table ITRO 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 criterion 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 2.

Table ITRO 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	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
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, 10.1-13.9 and 13.9 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, 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					
	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			

Category	Endpoints	24-Hour	Daytime[a]	Nighttime[b]	By Meal[c]
	Hourly median sensor glucose	X			
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
	LBGI: frequency and extent of low BG readings	X	X		X
	HBGI: frequency and extent of high BG readings	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: Premeal Glucose					
	Premeal Glucose				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 within 4 hours after meal(s)				X
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, 54-69 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, 54-69 and <70 mg/dL [3.0, 3.0-3.8 and 3.9 mmol/L]	X	X	X	X

Category	Endpoints	24-Hour	Daytime[a]	Nighttime[b]	By Meal[c]
	Duration (in minutes) of hypoglycemic episode (defined as at least 10 consecutive minutes <54 mg/dL [3.0 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 MMTT, and non-MMTT meals separately. Non-MMTT meals include all outpatient meals including morning (breakfast), midday (lunch) and evening (dinner) meals and overall (average across the 3 meals).

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 episodes during the following time interval after the start of each meal and overall will also be derived: <=1hr, <=2hr, >2 to <=4hr and <=4hr. The calculation will exclude any data collected after the next meal event.

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. In addition, only meals with the entire analysis interval (e.g., 0-1 hour after the start of the meal) on the same infusion set wear day will be included.

The meal time will be collected in the database by eCRF both for the MMTT and non-MMTT meals. The non-MMTT meals include all outpatient meals including morning (breakfast), midday (lunch) and evening (dinner) meals and overall (across the 3 meals). For the non-MMTT meals, only the first meal marker time will be used for each category (breakfast, lunch or dinner). Any data collected after the next meal (regardless of the category of the next meal) will be censored for the analysis with regards to the current meal. No outcome variables will be derived for bedtime meal but its time will be used to censor the data when deriving outcome variables for dinner. 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 0-4 hours.

All continuous variables will be analyzed using a similar MMRM model as used for the primary endpoint. If the percentage of patients with baseline missing (potentially due to missing meal event markers) is greater than 20% for any meal, a constrained longitudinal data analysis (cLDA) will be performed for all PPG-related CGM endpoints for that meal with treatment, strata (pooled country and patient's personal CGM use during the study), visit, and 2 dummy variables

to indicate treatment effect of LY90014 relative to Humalog at Visit 10 and Visit 13, respectively. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on LS means and Type III tests. SAS PROC MIXED will be used to perform the analysis. If this analysis fails to converge, the same order of the covariance structures will be tested as specified in Section 6.11.1.

Hypoglycemia/hyperglycemia rate per year as measured by CGM data will be analyzed using a negative binomial regression model with treatment as a covariate and an offset defined as the log transformation of days of CGM use/365.25 days. The proportion of patients with at least 1 hypoglycemia/hyperglycemia event as measured by CGM data (incidence) will be analyzed using a logistic regression model with treatment in the model. Similarly, proportion of patients who have achieved the guidance (Battelino 2019) recommended CGM targets of glycemic control (Table ITRO.6.6) during the 14 to 16 weeks of the treatment period will be summarized by treatment and analyzed using the same analysis methods.

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

Percentage of time with sensor glucose (24-hour)	Guidance Recommendation
target range	
70-180 mg/dL (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%

In addition, the following standardized glucose summary figures from the ambulatory glucose profile (AGP) will be generated, based upon the observed CGM data at baseline, Visit 10 and Visit 13:

- 24-hour period at individual patient level
- 24-hour period at the treatment level
- 0-4 hours relative to meal starting time at the treatment level, excluding data collected after the next meal event
- 0-4 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) at the treatment level, excluding data collected after the next meal event

6.14. Subgroup Analyses

6.14.1. Subgroup Analyses for HbA1c

The following subgroups will be analyzed using the efficacy estimand to evaluate consistency of treatment effects on the primary efficacy measure if there are sufficient numbers of patients in each treatment by subgroup (10% in each subgroup level):

- Age (<40 years, ≥40 years)
- HbA1c stratum (≤7.5%, >7.5%)
- Patient's personal CGM/FGM use during the study (yes/no)
- Sex (Male or Female)
- BMI (using the median as the cutoff)
- Bolus delivery speed at study entry
- Use of low glucose suspend
- Duration of diabetes (using the median as the cutoff)
- Duration of CSII use (using the median as the cutoff)
- Race
- Ethnicity
- Country
- Region
- Pump model series (500 Series [MiniMed 530G, MiniMed Paradigm Revel, MiniMed Paradigm Veo], 600 Series [MiniMed 630G, MiniMed 640G])

Analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 16) will be evaluated to assess the treatment by subgroup interaction. When analyzing HbA1c stratum (≤7.5%, >7.5%) as a subgroup the baseline HbA1c will be not be included as a covariate to avoid confounding.

6.14.2. Subgroup Analyses for Hypoglycemic Events

For documented hypoglycemia based on the thresholds of BG ≤70 mg/dL, the following subgroups will be analyzed using data collected from all randomized patients prior to discontinuation of IP through Week 16:

- Age (<40 years, ≥40 years)
- HbA1c stratum (≤7.5%, >7.5%)

- Patient's personal CGM/FGM use during the study (yes/no)
- Duration of diabetes (using the median as the cutoff)
- Duration of CSII use (using the median as the cutoff)
- Use of low glucose suspend
- Bolus delivery speed (standard, quick)
- Region

The event rate and incidence will be analyzed using the same model specified in Table ITRO.6.6 with the addition of factors for subgroup, and 2-way interaction of subgroup and treatment. The 2-way interaction will be used to evaluate treatment by subgroup interaction.

6.14.3. Subgroup Analyses for Unplanned Infusion Set Changes

For incidence and rate of unplanned infusion set changes, the following subgroups will be analyzed using data collected from all randomized patients.

- Bolus delivery speed at study entry
- Average of total daily dose during lead-in (using median as the cutoff)

6.14.4. Subgroup Analyses for CGM Data

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 from the CGM data, will be summarized for each treatment by patient's bolus delivery speed at study entry. If there are sufficient patients (≥10%) within each bolus delivery speed, an analysis will be performed using a MMRM model with treatment with bolus delivery speed and their interaction to assess the treatment by subgroup interaction.

6.15. 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.

7. Unblinding Plan

This is a double-blind study. LY900014 and Humalog treatment groups will have premeal bolus doses given via CSII. Investigators, patients, and study site personnel will be blinded to assigned dosing regimens throughout the study.

To preserve the blinding of the study, the Lilly study team will remain blinded throughout the study; only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. Unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from IP and should remain in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical research physician/clinical research scientist (CRP/CRS) prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

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9. Appendices

Appendix 1. Empirical Estimation of Relative Event Rate

Traditionally, Poisson distribution has been assumed to draw inference for the rate of rare events. When the event is rare and the sample size is large, it is known that the overall number of events is approximately from Poisson distribution. However, for some not very rare events such as severe hypoglycemic events in T1D patients, the total number of events may not be distributed from Poisson and may be over-dispersed. Assuming Poisson distribution may significantly underestimate the variance, and therefore may reduce the overage probability and inflate the Type-I error. An empirical method in estimating the variance of the relative event rate without assuming any distribution on the number of events will be provided in this appendix. Let X_{ij} denote the count response variable for patient *j* in treatment group *i*. Let $Y_i = \sum_j X_{ij}$ be the total number of events for treatment group *i*, and T_i denote the exposure for treatment group *i*. Let *i* = 0 for the control group and *i* = 1 for the experimental treatment group. The event rate for treatment group *i* can be calculated as

$$\hat{r}_i = \frac{Y_i}{T_i}$$

The empirical variance of $\hat{r}_i$ is

$$\widehat{Var}(\hat{r}_i) = T_i^{-2}\widehat{Var}(Y_i) = T_i^{-2} n_i S_i^2,$$

where S_i^2 is the variance of X_{ij} for treatment group *i*. Using the delta-method, the variance of $\log(\hat{r}_i)$ can be estimated as

$$\widehat{Var}(\log(\hat{r}_i)) = Y_i^{-2} n_i S_i^2$$

The relative rate of the experimental treatment versus the control treatment is estimated as

$$\hat{\lambda} = \frac{\hat{r}_1}{\hat{r}_0}$$

The variances of $\hat{\lambda}$ and $\log(\hat{\lambda})$ are

$$\widehat{Var}(\hat{\lambda}) = \hat{\lambda}^2 \widehat{Var}(\log(\hat{\lambda}))$$

$$\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right) = \widehat{Var}(\log(\hat{r}_0)) + \widehat{Var}(\log(\hat{r}_1)) = Y_0^{-2} n_0 S_0^2 + Y_1^{-2} n_1 S_1^2$$

Assuming $\log(\hat{\lambda})$ is asymptotically from a normal distribution, the $100(1-\alpha)\%$ confidence interval for $\log(\hat{\lambda})$ can be constructed as

$$\left[\log\left(\hat{\lambda}\right) - z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)},\ \log\left(\hat{\lambda}\right) + z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}\right]$$

Then, the $100(1-\alpha)\%$ confidence interval for $\hat{\lambda}$ is

$$\left[\hat{\lambda}\exp\left(-z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}\right),\qquad \hat{\lambda}\exp\left(z_{1-\frac{\alpha}{2}}\sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}\right)\right] \tag{1}$$

The p-value for testing the null hypothesis of $H_0: \lambda = 1$ is calculated as

$$p = 2\Phi\left(\left|\log\left(\hat{\lambda}\right)\right| / \sqrt{\widehat{Var}\left(\log\left(\hat{\lambda}\right)\right)}\right) \tag{2}$$

Appendix 2. Derivation of CGM Variables

General Derivation Specifications

All CGM variables will be derived for each patient, for each valid CGM day and also overall for baseline, Visit 10 (Week 6-8) and Visit 13 (Week 14-16).

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 (e.g., mean of daily difference [MODD]).

All CGM glucose derivations will be conducted in units of mg/dL and will be converted to mmol/L by multiplying by 0.0555.

Only readings from valid CGM days (defined in Section 6.13) collected between first dose and last dose of study drug (i.e., open-label Humalog used during the lead-in period or IP used during the treatment period) will be included in derivations, excluding data (if any) that are collected while patients temporarily are off pump or off study treatment.

The between-day variability, overall variability, and duration of hypoglycemia episode will be derived using all data collected across all valid CGM days, regardless of CGM days. For the other CGM variables, first determine the values within each day, then average across days within a visit.

The postprandial excursion related CGM variables (e.g., highest postprandial excursions, iAUC and mean sensor glucose) will be derived based upon the same excursion data.

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 (e.g., 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 hours, 18 hours, and 6 hours, 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 244 observations recorded in a 24-hour period, the percentage of time spent in hypoglycemia during the 24-hour period for this patient will be calculated as 15/244 = 6.15%. The duration (in minutes) with hypoglycemia (glucose value **<70** mg/dL [3.9 mmol/L]) during this 24-hour period for this patient will be calculated as the percentage times 1440 minutes (24 hours), (i.e., 15/244*288 = 17.7 minutes).

The percentage and duration in ranges during postmeal periods after the start of meals (MMTT, breakfast, lunch, and dinner) will also be derived.

Incremental Area under the Glucose Curve (iAUC)

iAUC0-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, and T could be 1 hr, 2 hr, 3 hr or 4 hr. 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 allows that the CGM measures in the window [-19,0] for G0 and [0+14] for GT fall on the previous or the next infusion set wear day.

Mean Sensor Glucose Excursions

Mean sensor glucose excursions in a postmeal time interval will be calculated by averaging all excursion values within the time interval where excursions are defined as G_i - G_0 as defined in iAUC.

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.
- Step 2: Count the number of distinct events over the 24-hour period.
- Step 3: Calculate rate per month by multiplying count by 365.25/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).

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

$\mathrm{BG}_{k,i}$ represents the glucose value at time point *i* on day *k* unless otherwise specified under MAGE definition.

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):

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

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

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

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

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

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,

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

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.

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.

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):

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

Between-day glucose coefficient of variation (CV):

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

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.

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

In addition to the CGM outcomes above, SD and CV in the daily mean values will also be derived.

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.

Risk for Hypo/Hyperglycemia

The LBGI has been developed to quantify 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

$\text{rl}\left(\text{BG}_i\right) = 10 \times \text{f}\left(\text{BG}_i\right)^2$ if $f(BG) < 0$; otherwise $rl(BG_i) = 0$

$\text{rh}\left(\text{BG}_i\right) = 10 \times \text{f}\left(\text{BG}_i\right)^2$ 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

$$BGRI = LBGI + HBGI$$

Daily CGM Data Summary

For daily CGM summary variables (Section 6.13), 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.

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 (see section "Incremental Area under the Glucose Curve [iAUC]") by multiplying the sum of trapezoids by (the length of the period)/ sum of time intervals calculated in the AUC).

Highest Postprandial Glucose

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.

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, truncating the data at the next meal event.

Other

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

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