ITSB SAP v3

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes PRONTO-Peds

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1. Statistical Analysis Plan: I8B-MC-ITSB: A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes PRONTO -Peds

LY900014

Study I8B-MC-ITSB is a Phase 3, prospective, randomized, outpatient, multinational, multicenter, parallel, active-controlled study conducted in children and adolescent patients with T1D currently using a MDI regimen.

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Protocol I8B-MC-ITSB
Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on 07 March 2019
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on 13 August 2020
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on 7 March 2019. This version was based on Protocol I8B-MC-ITSB approved on 26 October 2018, Protocol Addendum I8B-MC-ITSB(1) approved on 29 October 2018, and Protocol Addendum I8B-MC-ITSB(3) approved on 28 November 2018 and (3.1) amended on 06 March 2019.

Statistical Analysis Plan Version 2 was approved prior to the first unblinding of the study team. This version is based on Protocol I8B-MC-ITSB (b) approved on 30 Apr 2020, Protocol Addendum (3.2) approved on 24 Jan 2020, Addendum (4) approved on 06 March 2019, Addendum (5) approved on 14 June 2019 and Addendum (6) approved on 17 June 2019. The main types of changes are:

- Changing 2-sided significance level for tests of interactions between treatment groups and subgroup variables from 0.05 to 0.1
- Adding baseline and postbaseline definition table
- Adding description of subject disposition reporting during the lead-in phase due to re-screening. Protocol Amendment (b) allows one screening for subjects that failed screening or terminated before randomization due to COVID-19. Structure of some disposition table need to be modified to account for it.
- Changing the analysis population of the ITT estimand for the primary endpoint analysis to include all randomized patients, whether or not they have a postbaseline HbA1c assessment. The rationale is to follow the FDA guideline to include all randomized patients in the analysis.
- Adding a sensitivity analysis for the ITT estimand using an alternative imputation rule to account for patients with missing data due to COVID-19 related reasons.

Statistical Analysis Plan Version 3 was approved prior to the first unblinding of the study team. The main types of changes are:

- Adding a Kaplan-Meier plot of time to onset of the TEAE for TEAEs occurring in ≥1% of patients.
- Adding subgroup analyses using the ITT estimand for HbA1c.
- Adding use of personal CGM/FGM as a subgroup variable for the subgroup analyses of HbA1c and hypoglycemic events.
- Clarifying that site personnel and patients are unblinded to the open-label treatment group in the Unblinding Plan.

4. Study Objectives

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

Table ITSB.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 1 to <18 years of age with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin as part of a multiple daily injection regimen for 26 weeks	1. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Gated Objective	
2. To test the hypothesis that LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal, (LY900014+20), is noninferior to Humalog, administered as prandial insulin (0 to 2 minutes prior to the meal), on glycemic control (NIM=0.4% for HbA1c)	2. Change from baseline HbA1c values at Week 26
3. To test the hypothesis that LY900014 is superior to Humalog in improving glycemic control (HbA1c) when administered as prandial insulin (0 to 2 minutes prior to the meal).	3. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
4. To compare LY900014, LY900014 +20, and Humalog with respect to the incidence and rate of documented post-dose hypoglycemia	4. Rate (events/patient/year) and incidence (percent of patients with events) of documented post-dose hypoglycemic events within 1 and 2 hours after the prandial dose from Week 0 through Week 26
5. To compare LY900014, LY900014 +20, and Humalog with respect to the incidence and rate of documented hypoglycemia	5. Rate (events/patient/year) and incidence (percent of patients with events) of documented hypoglycemic events from Week 0 through Week 26
6. To compare LY900014, LY900014 +20, and Humalog on the rate of severe hypoglycemic events	6. Rate (events/patient/100 years) of severe hypoglycemic events from Week 0 through Week 26

Objectives and Endpoints

Objectives	Endpoints
7. To compare LY900014, LY900014 +20, and Humalog with respect to total, basal, and prandial insulin dose	7. Change from baseline in total, basal, and prandial insulin doses and prandial/total insulin dose ratios at Week 26
8. To compare LY900014, LY900014 +20, and Humalog with respect to the proportion of patients achieving HbA1c targets	8. The proportion of patients with HbA1c <7% and <7.5% at Week 26
9. To compare LY900014, LY900014+20, and Humalog with respect to 7-point SMBG	9. Change from baseline to Week 26 in 7-point SMBG values
Tertiary/Exploratory Objectives	
10. To compare LY900014, LY900014 +20, and Humalog with respect to changes in body weight	10. Change in weight (kg) from baseline to Week 26
11. To compare LY900014, LY900014 +20, and Humalog with respect to glycemic variability	11. Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 7-point SMBG profiles
12. To compare the incidence of treatment-emergent positive anti-insulin lispro antibodies for LY900014, LY900014 +20, and insulin lispro	12. Incidence of treatment-emergent positive anti-insulin lispro antibodies

Abbreviations: HbA1c = hemoglobin A1c; NIM = noninferiority margin; SMBG = self-monitored blood glucose; T1D = type 1 diabetes.

5. A Priori Statistical Methods

5.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter, Lilly). 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 this SAP and/or in the clinical study report (CSR). Additional exploratory analyses will be conducted, as deemed appropriate.

For purposes of analysis, the following populations are defined in Table ITSB.5.1:

Table ITSB.5.1. Patient Populations

Population	Description
Entered	All patients who sign informed consent.
Enrolled	All patients who receive at least 1 dose of open-label Humalog during the lead-in period
Randomized	All patients who are randomly assigned to study treatment at Visit 4. Treatment group will be defined on the basis of 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 on the basis of the treatment the patients are assigned.
Completer	Patients included in the Randomized Population who have completed Week 26 of study treatment without permanent discontinuation of IP. Treatment group will be defined on the basis of the treatment the patients are assigned.
Per Protocol	Patients included in the Randomized Population who have completed Week 26 of study treatment without permanent discontinuation of IP and without significant protocol deviations through Week 26 that would significantly impact the primary objective. Treatment group will be defined on the basis of the treatment the patients actually receive.
PedsQL	A subset of the Randomized Population who have an informed consent for the PedsQL addendum signed by parent(s)/legal guardian(s) and questionnaires completed at both baseline and post-baseline.
CGM	A subset of the Randomized population who have an inform consent for CGM addendum signed by parent(s)/legal guardian(s) and valid CGM data at baseline or post-baseline.

Abbreviation: CGM = continuous glucose monitoring; IP = investigational product; PedsQL = Pediatric Quality of Life.

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

Efficacy analyses will be conducted on all randomized patients according to the treatment the patients are assigned. The analyses for the primary and gated objectives will be performed for the efficacy estimand including data collected prior to permanent discontinuation of investigational product (IP) and for the intention-to-treat (ITT) estimand including all data collected regardless of IP use. The primary endpoint will also be analyzed using the Per Protocol (PP) and Completer populations.

Unless otherwise specified, the efficacy analyses for other secondary objectives and exploratory objectives will be performed for the efficacy estimand. When change from baseline is included as a response variable of analysis models, the patient will be included in the analysis only if a baseline and at least 1 postbaseline measurement are available, except for the analysis for ITT estimand on primary endpoint. The analysis for the ITT estimand will include all randomized patients with a baseline.

Safety analyses will be conducted on the Safety Population. Analyses of adverse events (AEs) will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data collected prior to permanent discontinuation of IP. The second set of analyses will include all data collected during the course of the entire study including the follow-up visit, regardless of IP use. Analyses of hypoglycemia will use data collected prior to permanent discontinuation of IP; while analyses for post-treatment may be performed as needed. Analyses of safety laboratory measurements will be performed on all data during the planned treatment period regardless of IP use.

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

- For data only measured at an office visit (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 AEs and hypoglycemia events from patient diary 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 day) will be considered as data on IP.
- For insulin dose data including both basal and prandial insulin dose, the dose used between the first IP dose date and the last IP dose date will be considered as data on IP.
- For the 7-point self-monitored blood glucose (SMBG) profiles, the profiles measured after the first IP dose date and prior to the last IP dose date will be considered as data on IP.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence interval (CI) 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 0.05. Countries in similar geographic regions with fewer than 10 patients, based on 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.

Table ITSB.5.2 shows the definition of baseline and post-baseline for each variable to be analyzed. The baseline variables are derived from the evaluable data during the baseline period.

Table ITSB.5.2. Baseline and Postbaseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Post-Baseline Observations
Lead-In Period			
HbA1c ANCOVA	All Randomized Patients	Visit 1	Visit 4 prior to initiation of IP
Basal, bolus, and total insulin doses, and bolus/total insulin dose ratios continuous analysis	All Randomized Patients	Not applicable	Visit 3-4
TEAE	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 if the dose date is missing)
26-Week Treatment Period (including Safety Follow-Up Visit where applicable)			
HbA1c ANCOVA (ITT estimand)	All Randomized Patients	Last of Visits 1-4	Visit 15 with imputation for patients who discontinue study prior to Visit 15
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 7, 10, and 15 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 7, 10, and 15 prior to discontinuation of IP
CGM outcomes	All Randomized Patients with at least one from baseline and post-baseline observations	Visit 4	Visit 15
Basal, bolus, and total insulin doses, and bolus/total insulin dose ratios continuous analysis	All Randomized Patients	Last of Visits 3-4	Visits 5-15 prior to discontinuation of IP

Baseline and Postbaseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Post-Baseline Observations
7-point SMBG	All Randomized Patients with a baseline and at least one post-baseline observation	Visit 4 prior to initiation of IP	Visits 10 and 15 prior to discontinuation of IP
Health outcomes (PedsQL)	All Randomized Patients with a baseline and a post-baseline observation	Visit 4	Visits 15 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	Last of Visits 1-4	Last of Visits 5-15 (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	Last of Visits 1-4	Visits 5-15 (including unplanned visits) regardless of IP use
Hypoglycemia events	Safety Population	All Visits 2-4	All Visits 5-15 prior to discontinuation of IP
Weight and vital signs	All Patients in the Safety Population with a baseline and a post-baseline observation	Last of Visits 1-4	Visits 7, 10, 12, 15 prior to discontinuation of IP
Anti-insulin lispro antibodies	Safety Population	Visit 4	Visits 7, 10, 15 regardless of IP use
TEAE	Safety Population	Prior to first dose of randomized IP (or v4 date if missing), after first dose of open label Humalog (or v2 date if missing)	From randomization to Week 26 prior to discontinuation of IP OR from randomization to safety follow-up

Abbreviations: ANCOVA = analysis of covariance; HbA1c = hemoglobin A1c; IP = investigational product; ITT = intention-to-treat; MMRM = mixed-effect repeated measures model; PedsQL = Pediatric Quality-of-Life; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event.

For continuous measures, summary statistics will include sample size, mean, standard deviation (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. 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 Système International (SI) units will be presented. Therefore, both % and mmol/mol will be presented for hemoglobin A1c (HbA1c) and both mg/dL and mmol/L will be presented for glucose measurements.

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

5.2. Adjustments for Covariates

Stratification factors of this study include country, HbA1c stratum (≤8.0%, >8.0%), type of basal insulin at randomization (insulin glargine, detemir or degludec), and age group (1 to <12, 12 to <18 years). Stratification factors will be entered into the interactive web-response system (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 in the database.

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

Other efficacy analyses will include the stratification factors as noted in Sections 5.11 and 5.12.

5.3. Handling of Dropouts or Missing Data

The analysis for the primary and gated objectives will be performed for the ITT estimand including all data collected through Week 26 regardless of IP use and the efficacy estimand including data collected prior to permanent discontinuation of IP through Week 26.

For the US Food and Drug Administration (FDA) submission, the ITT estimand will be used. For the analysis of HbA1c, imputation of missing data will be performed as described in Section 5.11.1.

For non-FDA submissions, the efficacy estimand will be used. The missing data will be addressed by using a mixed-effect model repeated measures (MMRM) analysis. The MMRM model provides consistent estimator when data are missing at random. The model implicitly adjusts for missing data through a variance-covariance structure. An ANCOVA model will also

be used in the analysis of HbA1c. Unless otherwise stated, missing endpoints will be imputed using the last-observation carried forward (LOCF) approach, using only postbaseline data.

5.4. Multicenter Studies

Countries in similar geographic regions with fewer than 10 patients, based on the 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.

5.5. Multiple Comparisons/Multiplicity

The test for superiority in HbA1c change from baseline (the second gated objective) will be conducted only when the test for noninferiority (the first gated objective) has been achieved. The gated objectives won't be conducted if the primary objective cannot be met.

No multiplicity test adjustment will be made for other objectives.

5.6. Patient Disposition

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

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 from randomization to the end of the study will be compared between treatment groups using Fisher's exact test.

Frequency counts and percentages of all patients entered and discontinued from the study prior to the lead-in period will be summarized for all entered patients. A similar summary will also be provided for the lead-in period using Enrolled Population.

A listing of the primary reason for treatment discontinuation 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 receive at least 1 dose of open-label Humalog during the lead-in period, the number of patients who are randomized to study treatment, and the number of patients who discontinue the study or study treatment during the 26-week treatment period.

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

I8B-MC-ITSB Protocol Amendment (b) allows 1 rescreening of patients who had a screen failure or unexpectedly had to discontinue before randomization due to COVID-19 enrollment pause. A listing will be presented to show the patient's previous patient number and current patient number. Disposition tables during the lead-in phase will be further classified such that rescreening is taken into account.

5.7. Patient Characteristics

A summary table will be generated for patient baseline characteristics using all randomized patients. The variables that will be included but not limited to include the following: age, age groups (age group 1:1 to <12, 12 to <18 years, and age group 2: 1 to <6, 6 to <12, 12 to <18 years), sex, country, ethnicity, race, height, weight, body mass index (BMI). For continuous variables, the following statistics will be provided: mean, SD, minimum, maximum, and median, and treatment groups will be compared using an analysis of variance 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 baseline will be provided.

A similar summary of diabetes characteristics will also be generated. The variables that will be included but not limited to include the following: duration of diabetes, the type of prandial insulin at screening, the type of basal insulin therapy at randomization, prandial insulin dosing plan (carbohydrate counting or pattern adjustment), HbA1c at screening and randomization, and HbA1c stratum.

The above summaries of baseline and diabetes characteristics will also be provided for patients who participate in the Pediatric Quality of Life addendum and complete the questionnaire both at baseline and post-baseline.

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), and the number and percentage of patients with preexisting conditions will also be summarized by treatment group using MedDRA PT. Historical conditions are conditions that end prior to first dose of IP and pre-existing conditions are conditions that are still ongoing at first dose of IP. Events will be ordered by decreasing frequency. No statistical comparisons between treatment groups will be performed.

5.8. Treatment Compliance

The time intervals between prandial insulin dose administration time and the start time of the corresponding meal will be summarized by treatment groups based on the following categories: pre-meal dosing, >0 to ≤10 minutes, >10 to ≤20 minutes, and >20 minutes after the start of the meal for individual visits during the treatment period.

5.9. Important Protocol Deviations

Important protocol deviations (IPD) that potentially compromise the data integrity and patients' safety will be summarized by treatment group for all randomized patients. The IPDs will be identified by site monitoring and statistical programming using the clinical database. Patients with more than one IPD from the same category, subcategory, and study specific term will only be counted once per patient.

The following may significantly impact the results of the primary objective:

- lack of informed consent
- missing HbA1c at the primary endpoint

Patients with 1 or more such deviations (lack of informed consent or missing HbA1c at endpoint) will be excluded from the PP population.

The listing of important protocol deviations for all randomized patients during the entire study, with the indication of whether to be excluded from the PP population, will also be provided. 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.

5.10. 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 period. 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.

A summary of previous diabetes therapies that were discontinued prior to informed consent will be generated for the Randomized Population. A summary of concomitant medication used during the lead-in period will also be provided for the Randomized Population.

5.11. Efficacy Analyses

5.11.1. Primary Outcome and Methodology

The primary objective of this study is to test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (noninferiority margin [NIM]=0.4% for HbA1c) in patients 1 to <18 years of age with T1D, when administered as prandial insulin, in combination with basal insulin for 26 weeks. There will be 2 primary analysis methods, each tested at the full significance level of 0.05.

For the US FDA submission (using the ITT estimand), all randomized subjects, regardless of their postbaseline result availability, will be included in the analysis. Due to COVID-19, patients are allowed to have their laboratory data collected at a local laboratory if there is any ongoing extenuating situation, such as travel restriction. HbA1c data collected from the local laboratory will be included in the analysis in the same way as those collected from the central laboratory. The missing endpoints will be imputed by the copy reference or the return to baseline approach. For the copy reference approach, the reference for each treatment group is from the retrieved dropout patients who discontinue IP but have the measurement at the primary endpoint in the same treatment group. If there are only a limited number of patients in the reference group that leads to a failure in performing the proposed multiple imputation analysis such that the model cannot converge, or the number of records in the reference group is less than the number of records with missing data, the missing endpoints will be imputed by the return to baseline

approach. For the return to baseline approach, the patient-level observed baseline value plus a noise will be used to impute the missing endpoints. 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 26 from individual non-missing HbA1c values at Week 26. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog from an ANCOVA. The model for the change from baseline to the Week 26 HbA1c endpoint will include treatment and strata (pooled country, type of basal insulin, and age group) as fixed effects and baseline HbA1c as a covariate. The final estimates will be the combined estimates from at least 1000 imputations.

For non-FDA submissions, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog at Week 26 (Visit 15) 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 26 (efficacy estimand). In contrast to the population of ITT estimand, randomized patients with a baseline and at least one postbaseline result will be included in the analysis. 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 (pooled country, type of basal insulin, and age group), 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.

5.11.2. Additional Analyses of the Primary Outcome

The primary MMRM analysis model will be repeated using the PP and Completer populations as a sensitivity analysis. If the conclusion differs from that of all randomized patients, the data and analyses will be further investigated.

A secondary analysis model for the efficacy estimand will be an ANCOVA for HbA1c change from baseline to the study primary endpoint, using the model with strata (pooled country, type of basal insulin, and age group) and treatment as fixed effects and baseline as a covariate. Missing endpoints will be imputed using the LOCF approach using postbaseline data only.

5.11.3. 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 of 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=0.4) will be included as a special case of the progressive stress test.

For the ITT estimand, the imputation of missing data will be as described for the FDA primary analysis, and ANCOVA on the change from baseline to Week 26 in HbA1c will be used.

For the efficacy estimand, the copy reference approach will be used to impute missing data and the reference group will be the Humalog treatment group. Imputation will be for all longitudinal visits.

Sensitivity Analyses for Missing Data due to COVID-19 pandemic:

Missing data due to the pandemic represents an extraordinary circumstance, and missing data could be more prevalent in some geographic regions than in others. Lilly has been following a mitigation plan that aims to reduce the impact from the pandemic. Nevertheless, Lilly expects missing data at the primary endpoint visit, Visit 15 HbA1c, for COVID-19 related reasons:

- COVID-19 infection (adverse event) or death caused by infection,
- Discontinuation of treatment due to COVID-19 related reasons,
- Discontinuation of study due to COVID-19 related reasons, and
- Completed the 26 week treatment period, but missed primary endpoint due to COVID-19 related reasons.

Given those extenuating circumstances, the imputation rule as described when introducing ITT estimand may not be appropriate because the team assumes these subjects were to adhere to the study procedure if not interrupted by the pandemic. Thus a sensitivity analysis will be performed by applying an alternative imputation rule. In particular, for these subjects, all available Visit 15 HbA1c values will be utilized to impute their primary endpoints, within each treatment arm. The original imputation rule will be applied to other patients. The process after the imputation is the same as that for ITT estimand.

5.11.4. Analysis of Gated Objectives

Gatekeeping strategy will be used to control the overall type I error for testing the following gated objectives: noninferiority of LY900014+20 to Humalog in change from baseline to the study primary endpoint in HbA1c and superiority of LY900014 compared with Humalog in change from baseline to the study primary endpoint in HbA1c.

Following the successful claim of the primary objective, the noninferiority between LY900014+20 and Humalog in HbA1c change from baseline will be assessed using the same approach for the primary objective (ITT estimand for FDA submission and efficacy estimand for non-FDA submissions) with a NIM of 0.4%. Only when the noninferiority between LY900014+20 and Humalog is demonstrated, the superiority of LY900014 in controlling HbA1c compared to Humalog will be assessed. The superiority assessment will be based on the above statistical approaches for the primary objective (ITT estimand for FDA submission and efficacy estimand for non-FDA submissions). If the upper limit of the 2-sided 95% CI is below zero, LY900014 will be declared superior to Humalog.

5.11.5. Other Secondary Efficacy Analyses

The analyses described in Section 5.11.5 to Section 5.11.7 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 26 will be analyzed using the same MMRM model as for the analysis of the primary outcome.

At each visit (including both telephone and office visits), the basal daily dose and prandial insulin dose at different time points (morning meal, mid-day meal, evening meal and other) taken 3 days prior to the visit will be collected in eCRF. The average daily basal insulin dose per visit for each patient will be used in the analysis. Similarly, the average prandial insulin dose for each meal category (ie, morning meal, mid-day meal, evening meal, snack, and other) will be calculated, and average daily prandial insulin dose calculated as the sum of these average prandial insulin meal doses will be used for analysis. If either average daily basal or average daily prandial insulin dose is missing, the total daily insulin dose and the prandial/total insulin dose ratio will be set as missing for analysis. The analyses of insulin dose (ie, actual and change from baseline in total, basal, prandial insulin dose and prandial/total insulin dose ratio), will use an MMRM model similar to that for the primary outcome with an additional term of HbA1c stratum ($\leq$8.0%, >8.0%).

Treatment comparisons for the proportion of patients with HbA1c <7.0% and <7.5% 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. As a sensitivity analysis, the proportion of patients with HbA1c <7.0% and <7.5% at Week 26 (Visit 15), imputed using LOCF, will be compared using a logistic regression model with terms for treatment and baseline HbA1c value.

Three 7-point SMBG profiles are expected to be collected during the 2 weeks prior to specified visits. For each time point, the average of the corresponding SMBG values from the SMBG profiles will be used for analysis. The analyses of the SMBG variables will use an MMRM model similar to that for the primary outcome with an additional term of HbA1c stratum (≤8.0%, >8.0%).

5.11.6. Health Outcomes Analyses

Patients and caregivers who are enrolled at sites in the US and who speak English will be asked to participate in Pediatric Quality of Life (PedsQL) addendum I8B-MC-ITSB(1). The PedsQL Population includes all randomized patients who have an informed consent for the PedsQL addendum signed by parent(s)/legal guardian(s) and completed PedsQL questionnaire at both baseline (Visit 4) and post-baseline (Visit 15 or early discontinuation [ED]). The PedsQL Population will be used for all analyses specified in this section.

Baseline demographics and characteristics of patients participating in the PedsQL addendum will be summarized by treatment. The PedsQL Generic Core and PedsQL 3.2 Diabetes Module will be scored according to the user manuals.

For the PedsQL Generic Core (4.0) (Varni et al. 2003) and PedsQL Diabetes (3.2) (Varni et al. 2013) scales, transformation of scores are needed as indicated by the scoring manual. Items are scored on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Items are then reversed scored as follows: 0=100, 1=75, 2=50, 3=25, 4=0. The dimension scores and the summary scores are calculated by summing the transformed scores of the items divided by the number of items answered. Moreover, for both the PedsQL Generic Core (4.0) and PedsQL Diabetes (3.2) scales, if more than 50% of the items in the scale are missing, then the Scale Scores should not be computed. If 50% or more items are completed, mean of the completed items in a scale will be used to impute the missing scores.

The PedsQL Diabetes (3.2) and PedsQL Generic Core (4.0) scales will be analyzed by ANCOVA model using treatment, strata (pooled country, type of basal insulin, and HbA1c stratum) as fixed effects and baseline score as a covariate. The analyses will cover the total scores, all subscale scores, and dimensions.

5.11.7. Analyses of Exploratory Objectives

The following endpoint derived from the 7-point SMBG profiles at each scheduled visit, will be analyzed using the MMRM model similar to that for the primary outcome with an additional term of HbA1c stratum (≤8.0%, >8.0%):

- 1-hour post-meal excursion
- between-day coefficient of variation (CV) and SD
- Within-day CV and SD

The excursion of SMBG will be calculated for each meal category (morning meal, midday meal, evening meal and all meals). The average value of excursions from the same visit for each patient will be used in the analysis.

Blood glucose (BG) values that are out of the detectable range (BG <20 mg/dL [1.1 mmol/L] or BG >600 mg/dL [33.3 mmol/L]) of the glucometer will be excluded from the analysis data. For baseline SMBG, records that are collected on or after the first dose date will be excluded from the analysis. If there are multiple records on the same day and same Timepoint, only the last entry will be used for variable derivation. BG readings without units will not be used in the analysis.

At a given visit, the CV and SD on each day with the 7-point 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 7 pre-specified SMBG time points will be calculated using the corresponding glucose values of the 7-point 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.

5.12. Safety Analyses

Safety measures will include AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to Humalog.

5.12.1. Extent of Exposure

Duration of exposure to study drug will be summarized. The following summary statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (ie, total patient-years of exposure). The number and proportion of patients falling into the following different exposure categories will also be summarized: <1 month (>0 and <30 days), ≥1 and <3 months (≥30 and <90 days), ≥3 and <6 months (≥90 days and <180 days), and ≥6 months (≥180 days).

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.

5.12.2. Adverse Events

Analyses of AEs will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data collected prior to permanent discontinuation of IP. The second set of analyses will include all data collected during the course of the entire study including the follow-up visit, regardless of IP use.

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 IP, the eCRF-collected flag will be used to determine whether the event started or worsened posttreatment.

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

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

The number and percentage of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT (regardless of SOC) and data collected prior to permanent discontinuation of IP. For each patient and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. No statistical comparison between treatment groups will be conducted.

The number and percentage of patients with common TEAEs (defined as ≥5% before rounding for LY900014 treated patients) will be summarized by treatment group using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency. Treatment will be compared by Fisher's exact test.

The number and percentage of patients who experienced a SAE including deaths and SAEs temporally associated or preceding deaths will be summarized by treatment group using MedDRA PT regardless of SOC. Events will be ordered by decreasing frequency. A listing of all SAEs will also be provided.

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

The number and percentage of patients who experienced other notable TEAEs (potential systemic hypersensitivity reaction, injection site reaction, and hepatic disorder) will be summarized by treatment group using all TEAEs regardless of IP use.

For events that are gender specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

For TEAEs occurring in ≥1% of patients, a Kaplan-Meier plot of time to onset of the TEAE will be presented.

Table ITSB.5.3 summarizes the planned analyses and the requirement of analysis data for different analysis periods. A "Yes" in the IP USE column indicates that only data collected prior to permanent discontinuation of IP will be included.

Table ITSB.5.3. Treatment-Emergent Adverse Event Analysis Periods

Analysis Period	Analysis Population	Analysis	IP USE	Treatment
Treatment Period (0-26 Weeks)	All patients in safety population	AE overview; TEAE by SOC and by PT; common TEAE; TEAEs by maximum severity; SAE; IP discontinuation due to AE; severe hypoglycemic events	Yes	LY900014, LY900014 +20, Humalog
Week 0 – Visit 801	All patients in safety population	AE overview; TEAE by SOC and by PT; common TEAE; SAE; other notable AEs (excluding severe hypoglycemic events); study discontinuation due to AE	All data regardless of IP use	LY900014, LY900014 +20, Humalog

Abbreviations: AE = adverse event; IP = investigational product; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

5.12.3. Deaths

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

5.12.4. Hypoglycemic Events and Other Adverse Events

The analysis plans for the following AEs are discussed in Section 5.12.4.1 through Section 5.12.4.4:

- hypoglycemic events
- systemic hypersensitivity reaction
- injection site reaction
- hepatobiliary events

5.12.4.1. Hypoglycemic Events

Hypoglycemia events that occur during the study will be captured in eCRF. Whenever hypoglycemia is suspected, the patient should record the BG value, any associated symptoms, and the treatment administered in patient diary.

A set of events will be considered as 1 event in analysis if the duration between adjacent events is within a 30 minute time window. 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 post-dose time frame will be selected. If there are still multiple events tied, the latest event will be selected.

The following types of hypoglycemia events will be analyzed: documented hypoglycemia (with BG ≤70 mg/dL [3.9 mmol/L] or BG <54 mg/dL [3.0 mmol/L]), severe hypoglycemia, nocturnal hypoglycemia, and non-nocturnal hypoglycemia (with BG ≤70 mg/dL [3.9 mmol/L] or BG <54 mg/dL [3.0 mmol/L]). Only severe hypoglycemia will be collected as an AE and all episodes of severe hypoglycemia will be considered as SAEs.

Table ITSB.5.4 provides detailed statistical methods for each endpoint related to hypoglycemia. For these analyses, hypoglycemia events prior to the discontinuation of IP will be summarized. Additional analyses for other types of hypoglycemic events not mentioned in the table and for the posttreatment period may be conducted as needed.

A listing of patients with at least 1 severe hypoglycemia reported (as SAE) after randomization 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 ITSB.5.4. Summary of Analyses for Endpoints Related to Hypoglycemia

Endpoint	Analysis Period	Statistical Method
Rate of hypoglycemic events (per patient per year) All Documented[a] Nocturnal[a] Non-Nocturnal (Documented and occurred between waking and bedtime)[a]	0-12, 0-26weeks	Negative binomial regression with treatment and age group as covariates, log (exposure/365.25 days) as the offset in the model.
Incidence of hypoglycemic events All Documented[a] Nocturnal[a] Non-Nocturnal (Documented and occurred between waking and bedtime)[a]	0-12, 0-26weeks	Logistic regression with treatment and age group as covariates.
Rate of post-dose hypoglycemic events (per patient per year) for all 3 main meals All Documented [a]	≤1, ≤2, ≤4, >4, and >2 to ≤4 hours after start of prandial insulin dose within 0-12, 0-26,weeks	Negative binomial regression with treatment and age group as covariates, log (exposure/365.25 days) as the offset in the model.
Incidence of post-dose hypoglycemic events for all 3 main meals All Documented [a]	≤1, ≤2, ≤4, >4,and >2 to ≤4 hours after start of prandial dose within 0-12, 0-26,weeks	Logistic regression with treatment and age group as covariates.
Rate of severe hypoglycemic events (per patient per 100 years)	0-12, 0-26weeks	Exposure adjusted rate 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	0-12, 0-26weeks	Proportion of patients with severe hypoglycemia will be reported. The treatment comparison will be based on a logistic regression model with treatment and age group as covariates.

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

5.12.4.2. Systemic Hypersensitivity Reaction

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

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

Specifically, need to perform the following: (1) any narrow or algorithmic term from any 1 of the 3 SMQs indicated above (ie, combined search across narrow and algorithmic portions of all 3 SMQs); (2) any narrow scope term within each SMQ, separately (ie, narrow SMQ search); (3) any term within each SMQ, separately (ie, 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 the 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.

5.12.4.3. Injection Site Reaction

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

For injection site reactions, the presence and severity of erythema, induration, pain, pruritus, and edema will be collected through the eCRF and will be summarized for each treatment. There will be no statistical comparison between treatments.

5.12.4.4. Hepatobiliary Events

5.12.4.4.1. Treatment-Emergent Potential Hepatic Disorder

The percentages of patients with treatment-emergent drug-related hepatic disorder events will be summarized and compared by treatment 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.

5.12.4.4.2. 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. Postbaseline value and the change from baseline (last nonmissing value before randomization) to postbaseline value at Week 26 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 CN and SI units.

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

5.12.4.4.3. 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 (0-26 weeks) will be summarized between treatment groups:

- The percentages of patients with postbaseline ALT measurement greater than or equal to 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 postbaseline value and for the following subcategories based on baseline value
    - The analysis of 3X ULN will contain 4 subcategories:
        - patients whose non-missing maximum baseline value is less than or equal to 1X ULN
        - patients whose maximum baseline value is greater than 1X ULN but less than 3X ULN
        - patients whose maximum baseline value is greater than or equal 3X ULN
        - patients whose baseline values are missing

  - The analysis of 5X ULN will be contain 5 subcategories:
    - patients whose non-missing maximum baseline value is less than or equal to 1X ULN
    - patients whose maximum baseline value is greater than 1X ULN but less than 3X ULN
    - patients whose maximum baseline value is greater than or equal to 3X ULN but less than 5X ULN
    - patients whose maximum baseline value is greater than or equal to 5X ULN
    - patients whose baseline values are missing
  - The analysis of 10X ULN will contain 6 subcategories:
    - patients whose non-missing maximum baseline value is less than or equal to 1X ULN
    - patients whose maximum baseline value is greater than 1X ULN but less than 3X ULN
    - patients whose maximum baseline value is greater than or equal to 3X ULN but less than 5X ULN
    - patients whose maximum baseline value is greater than or equal to 5X ULN but less than 10X ULN
    - patients whose maximum baseline value is greater than or equal to 10X ULN
    - patients whose baseline values are missing

- The percentages of patients with postbaseline AST measurement greater than or equal to 3X, 5X, and 10X the Covance ULN will be summarized for all patients with a postbaseline value and for subcategories based on baseline, as described above for ALT.
- The percentages of patients with post-baseline total bilirubin measurement greater than or equal to 2 times (2X) the Covance ULN will be summarized for all patients with a post-baseline value and the following 4 subcategories:
  - patients whose non-missing maximum baseline value is less than or equal to 1X ULN
  - patients whose maximum baseline value is greater than 1X ULN but less than 2X ULN
  - patients whose maximum baseline value is greater than or equal to 2X ULN
  - patients whose baseline values are missing

Baseline will be the maximum observation in the baseline 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.

5.12.5. Clinical Laboratory Evaluation

The data from safety laboratory measures will be summarized at Week 26 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 postbaseline 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 26 (planned tests including early discontinuation) 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 26 weeks) will be summarized for patients who have both baseline and at least 1 postbaseline 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 lab 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 5.12.4.4.2 and Section 5.12.4.4.3.

5.12.6. Vital Signs and Other Physical Findings

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

The measurements during the treatment period (0 to 26 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 (planned measurements including early discontinuation) during the treatment period. 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 at any time during the treatment period (0 to 26 weeks) 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 not meeting criteria for the high limit during the baseline period to a value meeting the criteria for the high limit at any time that meets the specified change amount during the treatment period. A treatment-emergent low result is defined as a change from a value not meeting criteria for the low limit during the baseline period to a value meeting the criteria for the low limit at any time that meets the specified change amount during the treatment period. Treatment comparison will be based on Fisher's exact test. Table ITSB.5.5 will be used to define the low and high limits and change thresholds.

Table ITSB.5.5. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement for Children and Adolescents

Age (years)		Systolic BP, mm Hg (Supine or sitting – forearm at heart level)	Diastolic BP, mm Hg (Supine or sitting – forearm at heart level)	Pulse/HR, bpm (Supine or sitting)
Infant <2	Low	≤70 and decrease ≥15	≤35 and decrease ≥10	<70 and decrease ≥25
	High	≥112 and increase ≥15	≥74 and increase ≥10	>190 and increase ≥25
Child 2-4	Low	≤75 and decrease ≥15	≤40 and decrease ≥10	<60 and decrease ≥25
	High	≥116 and increase ≥15	≥76 and increase ≥10	>160 and increase ≥25
Child 5-9	Low	≤80 and decrease ≥15	≤45 and decrease ≥10	<60 and decrease ≥25
	High	≥122 and increase ≥15	≥78 and increase ≥10	>150 and increase ≥25
Child 10-11	Low	≤85 and decrease ≥20	≤50 and decrease ≥10	<60 and decrease ≥25
	High	≥126 and increase ≥20	≥82 and increase ≥10	>140 and increase ≥25
Adolescent 12-14	Low	≤90 and decrease ≥20	≤50 and decrease ≥10	<50 and decrease ≥15
	High	≥136 and increase ≥20	≥86 and increase ≥10	>120 and increase ≥15
Adolescent 15-17	Low	≤90 and decrease ≥20	≤50 and decrease ≥10	<50 and decrease ≥15
	High	≥140 and increase ≥20	≥90 and increase ≥10	>100 and increase ≥15

Abbreviations: BP = blood pressure; HR = heart rate.

5.12.7. Immunogenicity

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro for all randomized patients since Visit 1 prior to the first dose of open label Humalog used during the lead-in. Therefore, the blood sample result at Visit 1 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 15.

5.12.7.1. 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 1) to post-baseline (post-Visit 1) in the anti-insulin lispro antibody level (percent binding). Treatment-emergent antidrug antibody can be subclassified 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 1) to postbaseline detected anti-insulin lispro
- treatment-boosted response: change from detected anti-insulin lispro at baseline (Visit 1) to postbaseline detected anti-insulin lispro antibody level (percent binding) at least 157% of the baseline value

The TEADA status will be determined using all data regardless of IP use. The number and percentage of patients with positive TEADA response any time during the treatment period will be summarized by treatment group. For patients with positive TEADA response any time during the treatment period, the number and percentage of patients with positive insulin cross-reactivity anytime during the treatment period, and the number and percentage of patients not meeting the TEADA criteria at Visit 15 (or last visit for patients who discontinue the study prior to Visit 15) will also be summarized by treatment group. Treatment groups will be compared by Fisher's exact test.

Both actual and change from baseline for the anti-insulin lispro antibody level in percent binding regardless of IP use will be summarized by scheduled visit prespecified in the protocol for patients with positive TEADA response anytime during the treatment period. The repeated measurement from Visit 1 to Visit 15 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 nonmissing observation prior to or at Visit 15 and the analysis of maximum percent binding during the treatment period.

A listing of anti-insulin lispro antibodies at each visit will be provided for the safety population. 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.

Subgroup analysis for the following selected efficacy and safety variables will be performed by TEADA status during the treatment period:

- hemoglobin A1c and change from baseline in HbA1c
- basal, prandial, and total insulin dose
- treatment-emergent injection site reaction and hypersensitivity reactions

- event rate of all documented hypoglycemic events (based on the threshold of BG ≤70 mg/dL)

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 up 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 subgroup analysis for insulin dose will use the MMRM model specified in Section 5.11.5 using the efficacy estimands. 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 incidence of treatment-emergent injection site reactions and hypersensitivity reactions will be analyzed by a logistic regression model including terms of treatment, subgroup, and treatment by subgroup interaction. All data regardless of IP use will be used for this analysis.

The negative binomial regression model specified in Table ITSB.5.4 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/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.

5.12.8. 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
- serious adverse events
- discontinuations from study (or study drug) due to AEs
- pregnancy

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

5.13. Subgroup Analyses

5.13.1. Subgroup Analyses for HbA1c

The following subgroups will be analyzed for HbA1c if there are sufficient numbers of patients per group (eg, at least 10% in each group) for both the ITT and efficacy estimands:

- age (age group 1: 1 to <12 versus 12 to <18 years and age group 2: 1 to <6, 6 to <12, and 12 to <18 years)
- Body Mass Index (BMI, <25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2)
- hemoglobin A1c stratum (≤8.0% versus >8.0%)

- sex (male versus female)
- duration of diabetes (using the median as the cut-off)
- race
- ethnicity
- country
- region
- type of basal insulin (glargine, degludec and detemir)
- prandial insulin dosing plan (carbohydrate counting or pattern adjustment)
- personal continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) use (yes, no)

For the ITT estimand, analyses for HbA1c and change from baseline in HbA1c will be performed using an ANCOVA model that includes the same fixed effects and baseline as a covariate given for the primary analysis model plus factors of subgroup and 2-way interaction of subgroup and treatment.

For the efficacy estimand, 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 will be evaluated to assess the treatment by subgroup interaction.

The subgroup interaction effect will be evaluated using a significance level of 0.10, unadjusted.

Additional subgroup analyses may also be performed.

5.13.2. Subgroup Analyses for Hypoglycemic Events

For the documented hypoglycemia based on the threshold of BG ≤70 mg/dL, the following subgroups will be analyzed:

- age (age group1: 1 to <12 years and 12 to <18 years, and age group 2: 1 to <6, 6 to <12, and 12 to <18 years)
- hemoglobin A1c stratum (≤8.0% versus >8.0%)
- region
- type of basal insulin (glargine, degludec, and detemir)
- prandial insulin dosing plan (carbohydrate counting or pattern adjustment)
- personal CGM/FGM use (yes, no)

The event rate and incidence will be analyzed using the same model specified in Table ITSB.5.4 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.

5.14. 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.

A data and safety monitoring committee (DMC) consisting of pediatric experienced members external to the study team will review interim safety results at least once during the study. The DMC comprises those individuals responsible for the evaluation and interpretation of the results from the safety analysis. The DMC for this study will be conducted as an independent DMC. Therefore, the members of the DMC are external to Lilly. Further details pertaining to the DMC activities may be found in the DMC charter. Only safety analyses will be conducted for DMC review, no efficacy analysis will be conducted. The analyses for DMC will neither be reported to study team nor change the study design.

5.15. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

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

Adverse event reporting is consistent with other document disclosures (for example, the CSR, manuscripts, and so forth).

6. Unblinding Plan

6.1. Safety Monitoring

An independent DMC will have the responsibility to review the safety results in order to monitor safety of the patients in the study until the last patient completes the treatment period. Members will not have contact with anyone involved in the clinical care of patients and/or enrolled in this study in any way that could compromise the integrity of study. A limited number of preidentified individuals external to the study team will perform the data analysis for the DMC using the limited unblinded data. The detailed analysis and communication plan for the analyses will be defined in a separate DMC charter.

6.2. Site Level Unblinding

Investigators, patients, and study site personnel will be blinded to the double-blind treatment groups throughout the study. Investigators, patients, and study site personnel will be unblinded to the open-label treatment group.

The following applies to the double-blind treatment groups:

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. All calls/website visits resulting in an unblinding event are recorded and reported by the IWRS.

The investigator should make every effort to contact the Lilly clinical research physician or designee prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

If an investigator, site personnel performing assessments, or patient is unblinded during the double-blinded period, the patient must discontinue the IP and will be encouraged to continue in the study (Protocol Section 8.1).

6.3. Sponsor/Trial Level Unblinding

The study team will remain blinded to treatment assignments until all patients have completed the study and the database has been locked.

7. References

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8. 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 traditional method 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

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

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

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

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

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

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

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

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

Appendix 2. Statistical Analysis Plan for Continuous Glucose Monitoring (CGM)

Continuous glucose monitoring (CGM) will be performed in a subset of patients in Study I8B-MC-ITSB (ITSB) in order to evaluate the 24-hour glucose profile captured with CGM for LY900014 and Humalog, when either is used in combination with basal insulin as part of a multiple daily injection regimen. In 2 of the treatment groups, LY900014 and Humalog will be administered immediately (0 to 2 minutes) prior to each meal in a double-blind manner. A third open-label treatment group consists of LY900014 administered up to 20 minutes after the start of a meal (LY900014 +20). These 3 treatment groups are denoted as LY900014, Humalog and LY900014+20 in the study objectives.

This appendix provides the statistical analysis plan for the CGM addendum I8B-MC-ITSB(3.1). The target range for #3 objective has been changed from "71 to 180 mg/dL" to "70 to 180 mg/dL" to reflect the recommendations set forth in the "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range" (Battelino et al. 2019). Similarly, one of the cut points for #5 objective has been changed from "≤ 70 mg/dL" to "< 70 mg/dL."

Appendix 2.1. Objectives and Endpoints for CGM Addendum

Table APP.2.1 shows the objectives and endpoints for CGM addendum.

Table APP.2.1. Objectives and Endpoints for CGM Addendum

Objectives	Endpoints
Primary Objective	
1. To compare LY900014 and Humalog, when administered as prandial insulin (0 to 2 minutes prior to the start of a meal), with respect to the incremental glucose AUC0-2hours after the start of meals	1. Incremental AUC0-2hours after the start of meals from up to 10 days of continuous glucose monitoring (CGM) use at Week 26
Secondary Objective	
2. To compare LY administered as postprandial insulin up to 20 minutes after the start of a meal (LY900014 +20) and Humalog with respect to the incremental AUC0-2hours after meals	2. Incremental AUC0-2hours after the start of meals from up to 10 days of continuous glucose monitoring (CGM) use at Week 26
3. To compare LY900014, LY900014 +20 and Humalog with respect to the duration of time glucose values are within target range 70 to 180 mg/dL (3.9 and 10.0 mmol/L) during daytime.	3. Duration (in minutes) and percentage of time with glucose values within target range 70 to 180 mg/dL (3.9 and 10.0 mmol/L) during daytime, both inclusive, normalized to daytime period from up to 10 days of CGM use at Week 26
4. To compare the glucose excursions after meal between LY900014, LY900014 +20, and Humalog	4. Average glucose excursions 0 to 1, 2, 3, 4 hours after the start of meals, from up to 10 days of CGM use at Week 26

Objectives and Endpoints for CGM Addendum

Objectives	Endpoints
5. To compare LY900014, LY900014 +20, and Humalog with respect to the duration of time spent in hypoglycemic glucose ranges	5. 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 from up to 10 days of CGM use at Week 26
6. To compare LY900014, LY900014 +20, and Humalog with respect to the duration of time spent in hyperglycemic glucose ranges	6. Duration (in minutes) and percentage of time with glucose values >180 mg/dL (10.0 mmol/L) normalized to a 24-hour period from up to 10 days of CGM use at Week 26
7. To compare LY900014, LY900014 +20, and Humalog with respect to the glucose variability during daytime	7. Blood glucose risk index during daytime from up to 10 days of CGM use at Week 26

Appendix 2.2. General Considerations

The Dexcom G6® Continuous Glucose Monitoring System (Dexcom G6) will be used in CGM addendum I8B-MC-ITSB(3.1). Patients who choose to participate in the Study ITSB CGM addendum (3.1) will use the Dexcom G6 system during 2 periods of time, prior to baseline and prior to the 26-week primary endpoint. The Dexcom G6 will be worn for up to 10 consecutive days per period.

The CGM Population includes all randomized patients who have an inform consent for the CGM addendum signed by parent(s)/legal guardian(s) and valid CGM data at baseline (Visit 4) or primary endpoint (Visit 15). Unless otherwise specified, the analyses of the CGM addendum will use the CGM Population. The data collected after permanent discontinuation of investigational product or during days when patients are temporarily off study treatment will be excluded. There will be no multiplicity adjustment.

To ensure that the CGM outcome variables are only calculated from valid CGM days with sufficient data within the 24-hour, the following criterion will be used to determine a valid CGM day: minimum number of measures per day – at least 70% of the total measures (288 measures per day) that are supposed to be obtained. All the CGM derivations are based on the data from the valid CGM days with sufficient data defined above unless otherwise specified.

Patients will be instructed to capture the start time of 3 main meals (morning meal, mid-day meal, evening) when accompanied by prandial insulin dose during each CGM session in the patient CGM diary page. The start time will be used to derive the CGM meal related outcomes for each meal and across all meals. On valid CGM days, the meal related outcomes will also use the 70% cut-point to determine a valid CGM session for the variable derivation. For example, the $iAUC_{0\text{-}2hr}$ after the morning meal for a day requires at least 70% of the 24 measures (ie, at least 17 measures) during the 2 hour time window after the start of the morning meal. If the analysis time window covers the start time of the next meal (assuming *TN0* relative to the start time of the given meal and $TN0 < T$) and the number of non-missing measures within 0 to *TN0* is greater than 70% of measures within 0 to *T*, the derivation of the meal related outcomes within 0 to *T*

will be based on the data from time 0 to *TN0*. Only the first meal of each type per day will be included in derivations

All CGM outcome variables will be derived for each patient for each visit, based on the valid CGM data described above. The data will be summarized by visit and by treatment group.

For continuous measures, summary statistics will include sample size, mean, standard deviation (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 provided. Treatment comparisons will be evaluated by the treatment difference LS means, the 95% CIs for the treatment differences, and 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, unless otherwise specified.

A listing of all randomized patients with CGM addendum-specific informed consent form and did or did not wear the blinded Dexcom G6 at least once during the study will be produced. The listing will contain the dates that patients started and stopped wearing the Dexcom G6 for each visit during the study.

Additional analyses not specified in this SAP may be conducted, if deemed necessary.

Appendix 2.3. Baseline Characteristics

The following analyses planned for the main study (Section 5.7) will be repeated for the CGM Population:

- summaries of baseline and diabetes characteristics
- a listing of patients whose stratification factor value entered into the interactive web-response system (IWRS) is different from the clinical database
- a listing of patient characteristics at baseline

Appendix 2.4. Primary CGM Outcome and Methodology

The primary outcome of the CGM addendum is the iAUC0-2hr after meals obtained from up to 10 days of CGM use at Week 26. The derivation of the iAUC0-2hr for each visit is outlined in Appendix 2.8.

An ANCOVA model with treatment, type of basal insulin, hemoglobin A1c (HbA1c) stratum [≤8.0% or >8.0%], and age group as fixed effects and baseline as a covariate will be used for treatment group comparison. At Week 26, the treatment difference and LS mean of the difference estimated from the model will be provided.

If the percentage of the patients with missing baseline values is higher than 20% of the CGM Population, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead. An unstructured covariance structure will be used to model the within-patient

errors. If this analysis fails to converge, the following covariance structures will be tested in order:

- compound symmetry with heterogeneous variances
- compound symmetry without heterogeneous variances.
- First order autoregressive

The first covariance structure that converges will be used. The Kenward–Roger approximation will be used to estimate denominator degrees of freedom.

Appendix 2.5. Secondary CGM Variables and Analysis

The following variables will be derived from the original data collected through the CGM device and will be compared LY900014, LY900014+20 and Humalog at Week 26 using the similar model as the primary analysis in Appendix 2.4:

- incremental AUC 0-2 hours after the start of meals (across all three main meals)
- 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) during daytime (defined as 0600 to midnight), normalized to a 24-hour period
- average glucose excursions 0 to 1 hour after the start of meals (across all 3 main meals)
- average glucose excursions 0 to 2 hours after the start of meals (across all 3 main meals)
- average glucose excursions 0 to 3 hours after the start of meals (across all 3 main meals)
- average glucose excursions 0 to 4 hours after the start of meals (across all 3 main meals)
- duration (in minutes) and percentage of time with glucose values <54 (3.0 mmol/L) normalized to a 24-hour period
- duration (in minutes) and percentage of time with glucose values <70 mg/dL (3.9 mmol/L) normalized to a 24-hour period
- duration (in minutes) and percentage of time with glucose values >180mg/dL, (10.0 mmol/L) normalized to a 24-hour period
- blood glucose risk index during daytime (0600 to midnight)

Appendix 2.6. Additional Analyses

The following key efficacy and safety outcomes collected in the main study (not through CGM addendum) will be analyzed using the CGM Population:

- HbA1c at Week 26
- incidence and rate of documented hypoglycemic events from Week 0 to Week 26
- incidence and rate of nocturnal hypoglycemic events from Week 0 to Week 26
- incidence and rate of non-nocturnal hypoglycemic events from Week 0 to Week 26s
- incidence and rate of severe hypoglycemic events from Week 0 to Week 26

- change from baseline in total, basal and prandial insulin dose, and the ratio of prandial and total insulin dose at Week 26

The analysis methods for the above outcomes will be the same as those specified in Section 5.

Proportion of patients who have achieved the guidance (Battelino et al. 2019) recommended CGM targets of glycemic control (see Table APP.2.2) at Week 26 will also be summarized by treatment and analyzed using logistic regression model with treatment, age group and baseline as covariates.

Table APP.2.2. 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%

Appendix 2.7. Ambulatory Glucose Profile

The following standardized glucose summary reports from ambulatory glucose profile (AGP) will be generated, at treatment-group level and individual patient level by visit, based upon the observed CGM measures:

- 24-hour period
- 0 to 4 hours relative to meal starting time for morning meal, midday meal, evening meal and across all meals.

Appendix 2.8. Derivation for CGM Variables

By-meal CGM outcome variables will be derived for each meal and across all meals based on the valid CGM sessions (Appendix 2.2).

If any concentration below lower limit of quantification (LOQ) or above upper LOQ are identified, they will be treated as LOQ for calculation of the CGM parameters. No missing CGM values will be imputed.

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

All CGM glucose derivations will be conducted in units of mg/dL and mmol/L will also be provided by the conversion factor of 0.0555 from mg/dL.

Appendix 2.8.1. Incremental Area under The Glucose Curve (iAUC)

For a valid CGM meal session (with at least 70% of measures during the 0 to T hour[s] after the start of a specific meal) on a valid CGM day, $i\text{AUC}_{0-T}$ will be calculated as the sum of areas of all individual trapezoids within the time frame:

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

where G_i is glucose value at a particular time, G_0 is the glucose level before the start of the given meal (using the average values within the time window [-19, 0] minutes relative to the start of the meal), $\Delta \boldsymbol{t_i}$ is the time interval between consecutive glucose measures, k is the total number of trapezoids within the time frame 0-T and G_k is the glucose level at the end of the time frame 0-T (using the average values within the time window [0, 14] minutes relative to the last time point of the time frame). The derivation require that G_0 and G_k values are both available and the next meal starts after the end of the time frame 0-T.

$i\text{AUC}_{0-T}$ will be calculated for valid meal sessions and the average of a visit will be used in the analysis.

Appendix 2.8.2. Average Glucose Excursions

Average glucose excursions 0 to T hour(s) for each valid CGM meal session, will be calculated by averaging the excursions within the time frame 0-T and prior to the start time of next meal. The pre-meal glucose will use the average value within the time window [-19, 0] minutes relative to the start of the meal. The excursion at time T is calculated by deducting the glucose at time T by pre-meal glucose.

The average value from all valid CGM meal sessions at the same visit will be used in the analysis.

Appendix 2.8.3. Area under The Curve

Area under the curve (AUC) will be calculated using the standard trapezoidal rule by summing the trapezoid areas between two consecutive glucose measures in the prespecified time period (eg, 24-hour, or 1 hour after the morning meal).

Similar to $iAUC_{0-T}$, corresponding AUC_{0-T} will be derived. When the analysis time window covers the start time of the next meal and the number of non-missing measures satisfies the required minimum number, standardized AUC_{0-T} will be derived.

Appendix 2.8.4. Between-Day Glucose Variability

The notation below is for both between-day and within day glucose variability derivation:

i represents a time point within a time period (a 24-hour period, daytime or nighttime[defined as midnight to 0600])

n represents the number of time points within the time period

k represents a valid CGM day within a visit

m represents number of valid CGM days at a visit

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

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

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

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

Between-day glucose coefficient of variation (CV) [Clarke and Kovatchev 2009]:

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

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.

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

Appendix 2.8.5. Within-day glucose variability

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

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

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

Within-day glucose CV (Clarke and Kovatchev 2009):

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

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

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

The low blood glucose index (LBGI) has been developed to quantitate both frequency and severity of hypoglycemia. The LBGI has been validated as a predictor of severe hypoglycemia. 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 high blood glucose index (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 blood glucose risk index (BGRI) will be derived for each valid CGM day of a visit in the following steps:

Step 1: For each blood glucose (BG [mg/dL]) at the i^{th} time point, compute the following:

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

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

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

Step 2: Compute BG risk for each reading

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

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

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

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

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

Step 3: Compute LBGI and HBGI

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

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

Step 4: Compute BGRI

BGRI = LBGI + HBGI

The visit averages of LBGI, HBGI and BGRI will be calculated.

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

$$MAGE_k = \frac{\sum_{l=1}^{p} \left| BG_{k,l} - BG_{k,l-h} \right|}{p}$$

where,

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

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

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

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

Appendix 2.8.6. Glucose in Target Ranges, Hypoglycemia - or Hyperglycemia

The percentage of time within a glucose range (target, hypo- or hyperglycemia ranges) will be calculated as the number of observations within the specified range divided by the number of

observations in the time interval (eg, 24-hour period) on all valid CGM days at the same visit. The duration (in minutes) within the glucose range will then be calculated as the percentage of time within the glucose range times the length of the period (24 hour, 18 hour, and 6 hour, for the periods of 24-hour, daytime or nighttime, respectively).

For example, if a patient had a total of 13 observations with glucose values ≤70 mg/dL (3.9 mmol/L) out of a total of 270 non-missing observations recorded during the 24-hour period across a valid CGM day (with missing observations <30% of 288 measures per day) , the percentage of time spent in hypoglycemia during the 24-hour period for this patient on this day will be calculated as 13/270 = 4.8%. For a visit, the average percentage across all valid CGM days during the visit will be calculated and used for the calculation of the duration (in minutes) with hypoglycemia (glucose value ≤70 mg/dL [3.9 mmol/L]) during the 24-hour period for this patient by multiplying the average percentage with 1440.

Appendix 2.8.7. Hypoglycemic/Hyperglycemic Episodes

Hypoglycemic/hyperglycemic episodes 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. For each visit, count the total number of events occurred on the valid CGM days.

Appendix 2.8.8. Maximum Postprandial Glucose

Maximum postprandial glucose was the highest glucose within 4 hours after morning meal/midday meal/evening meal on a valid CGM day.

Maximum glucose excursion was the highest glucose excursion within 4 hours after morning meal/midday meal/evening meal on a valid CGM day.

Time to the maximum glucose was the time to the first maximum glucose value within 4 hours after morning meal/midday meal/evening meal on a valid CGM day.

Appendix 2.9. List of Derived CGM Variables

The following variables will be derived based on valid CGM data and derivation method defined in Appendix 2.2 and Appendix 2.8 respectively.

- Incremental $AUC_{0\text{-}1hour}$, $AUC_{0\text{-}2hours}$, $AUC_{0\text{-}3hours}$, $AUC_{0\text{-}4hours}$ after the start of morning meal, midday meal, evening meal and all three meals during each CGM section up to 10 days
- Average glucose excursion 0 to 1, 2, 3, 4 hours after the start of morning meal, midday meal, and evening meal and all three meals during each CGM section up to 10 days
- Maximum glucose excursion within 4 hours after the start of morning meal, midday meal, evening meal and all three meals
- Maximum glucose within 4 hours after the start of morning meal, midday meal, evening meal and all three meals
- Time to the maximum glucose within 4 hours after the start of morning meal, midday meal, evening meal and all three meals

- Area under the curve for a 24-hour, daytime and nighttime period
- Area under the curve during the 1, 2, 3, 4 hours after the start of morning meal, midday meal, evening meal and all three meals corresponding to above iAUC
- Between-day glucose variability during a 24-hour, daytime and nighttime period
    - standard deviation
    - coefficient of variation
    - mean of daily differences
- Within-day glucose variability during a 24-hour, daytime, nighttime period and 0-4 hour during morning meal, midday meal, evening meal and all three meals
    - standard deviation
    - coefficient of variation
    - Inter-quartile range
    - low blood glucose index
    - high blood glucose index
    - blood glucose risk index
    - mean amplitude of glycemic excursions (MAGE-, MAGE+ and MAGE+/- combined)
- Duration (in minutes) and percentage of time with glucose values within target range 70 to 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive for a 24-hour, daytime and nighttime period
- Duration (in minutes) and percentage of time with glucose values within target range 70 to 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive for 0-1, 0-2, 0-3, 0-4 hours during morning meal, midday meal, evening meal and all meals
- Duration (in minutes) and percentage of time with glucose values within target range 70 to 140 mg/dL (3.9 and 7.8 mmol/L), both inclusive for a 24-hour, daytime and nighttime period
- Duration (in minutes) and percentage of time with glucose values within target range 70 to 140 mg/dL (3.9 and 7.8 mmol/L), both inclusive for 0-1, 0-2, 0-3, 0-4 hours during morning meal, midday meal, evening meal and all meals
- Duration (in minutes) and percentage of time with glucose values within target range 54 to 69 mg/dL (3.0 and 3.8 mmol/L), both inclusive for a 24-hour, daytime and nighttime period
- Duration (in minutes) and percentage of time with glucose values within target range 181 to 250 mg/dL (10.1 and 13.9 mmol/L), both inclusive for a 24-hour, daytime and nighttime period
- Duration (in minutes) and percentage of time with glucose values <54 and (less than) 70 mg/dL (3.0 and 3.9 mmol/L) for a 24-hour, daytime and nighttime period
- Number of hypoglycemic episodes, defined as at least 10 consecutive minutes < 54 and <(less than) 70 mg/dL (3.0 and 3.9 mmol/L) during up to 10 valid CGM days
- Duration (in minutes) and percentage of time with glucose values >180 and >250 mg/dL (10.0 and 13.9 mmol/L) for a 24-hour, daytime and nighttime period
- Number of hyperglycemic episodes, defined as at least 10 consecutive minutes >180 and >250 mg/dL (10.0 and 13.9 mmol/L) during up to 10 valid CGM days

- Ambulatory Glucose Profile for 0 to 4 hours after the start of morning meal, midday meal, evening meal and all meals
- Ambulatory Glucose Profile for the 24-hour window
- Ambulatory Glucose Profile at individual patient level
- Duration (in minutes) of each individual hypoglycemic episode defined as at least 10 consecutive minutes < 54 and $\leq$(less than)70 mg/dL (3.0 and 3.9 mmol/L)
- Duration (in minutes) of each individual hyperglycemic episode defined as at least 10 consecutive minutes >180 and >250 mg/dL (10.0 and 13.9 mmol/L)
- Number of valid CGM days for each visit

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