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

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro With an Open-Label Postprandial LY900014 Treatment Group, in Combination With Insulin Glargine or Insulin Degludec, in Adults With Type 1 Diabetes PRONTO-T1D

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1. Statistical Analysis Plan: I8B-MC-ITRM: A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro with an Open-Label Postprandial LY900014 Treatment Group, in Combination with Insulin Glargine or Insulin Degludec, in Adults with Type 1 Diabetes PRONTO-T1D

LY900014

Study I8B-MC-ITRM is a Phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter, 3-treatment group, parallel, active-controlled study conducted in patients with type 1 diabetes currently using a multiple daily injection regimen.

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Protocol I8B-MC-ITRM
Phase 3

Statistical Analysis Plan version 1 electronically signed and approved by Lilly on 07 July 2017
Statistical Analysis Plan version 2 electronically signed and approved by Lilly on 27 March 2018
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 prior to the first patient visit on 7 July 2017. Version 1 was based on the Protocol I8B-MC-ITRM (ITRM) approved on 16 February 2017 and amended on 22 May 2017.

Statistical Analysis Plan (SAP) Version 2 was approved on 27 March 2018. The main types of changes are:

- adding analysis details (for example, analysis population or period, on investigational product (IP) data versus all data regardless of IP use), derivations (for example, derivations for 10-point self-monitored blood glucose [SMBG]-related and insulin dose-related variables), and rules (for example, to define unique hypoglycemia events)
- modifying analysis input data scope: for the continuous analysis of clinical laboratory tests, unplanned measurements are excluded from analysis to reduce bias (Computational Science Symposium Development of Standard Scripts and Programming Working Group 2013 [WWW])
- deleting the following analyses:
    - treatment-emergent adverse events (TEAE) by Preferred Term (PT) summary using all data regardless of IP use, because the by System Organ Class (SOC) summary and the common TEAE by PT summary together are sufficient
    - notable TEAE summary using on IP data, because the summary using all data regardless of IP use and the summary of its drug-related subset are more clinically relevant
    - malignant neoplasm TEAE summary, due to the expected low incidence rate; the analysis will be performed at the compound or integration level
    - hypoglycemia summaries for postmeal hypoglycemia <54 mg/dL because they are expected to be few thus less clinically relevant compared with other types of hypoglycemia events planned for analysis
    - hypoglycemia summaries for postmeal all documented and documented unspecified hypoglycemia because the information of time relative to meal is missing for documented unspecified hypoglycemia events

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

- replacing the imputation method with United States (US) Food and Drug Administration (FDA) -recommended “return to baseline” imputation method when the number of patients who discontinued IP but complete the study procedure without missing data is insufficient

- adding the on-IP definition for mixed-meal tolerance test (MMTT) for which the 14-day rule is not applicable
- removing analysis of limited clinical relevance or information (for example, vital sign analysis for the lead-in period was updated to be performed for weight only)
- adding or clarifying analysis details (for example, defining region for subgroup analysis, removing contradictory statements, explaining how to handle important protocol deviation duplicates)

4. Study Objectives

Table 4.1 shows the objectives and endpoints of the study. Week 52 endpoints for the secondary objectives only apply to the blinded treatment arms of LY900014 and insulin lispro.

Table 4.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
1. (H1) To test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control (NIM=0.4% for HbA1c) in patients with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec for 26 weeks	1. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Multiplicity Adjusted Objectives	
2. (H2) To test the hypothesis that LY900014 is superior to insulin lispro in controlling 1-hour PPG excursions, when administered as prandial insulin	2. Difference between LY900014 and insulin lispro in the 1-hour PPG excursion (serum glucose measured 1 hour after the start of the meal minus fasting serum glucose) from a MMTT at Week 26
3. (H3) To test the hypothesis that LY900014 is superior to insulin lispro in controlling 2-hour PPG excursions, when administered as prandial insulin	3. Difference between LY900014 and insulin lispro in the 2-hour PPG excursion (serum glucose measured 2 hours after the start of the meal minus fasting serum glucose) from an MMTT at Week 26
4. (H4) To test the hypothesis that LY900014 is superior to insulin lispro on improving glycemic control (HbA1c) when administered as prandial insulin	4. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
5. (H5) To test the hypothesis that LY900014 administered as postprandial insulin 20 minutes after the start of a meal, (LY900014+20), is noninferior to insulin lispro, administered as prandial insulin, on glycemic control (NIM=0.4% for HbA1c)	5. Difference between LY900014+20 and insulin lispro in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
6. To compare LY900014+20 with insulin lispro and LY900014 with respect to 1-hour and 2-hour PPG excursions	6. 1- and 2-hour PPG excursions from an MMTT test at Week 26
7. To compare the glycemic control of LY900014 with LY900014+20	7. Change from baseline HbA1c values at Week 26
8. To compare LY900014, LY900014+20, and insulin lispro on the rate of severe hypoglycemic events	8. Rate (events/patient/100 years) of severe hypoglycemic events from baseline through Week 26 and Week 52

Objectives and Endpoints

Objectives	Endpoints
Other Secondary Objectives (continued)	
9. To compare LY900014, LY900014+20, and insulin lispro with respect to the incidence and rate of documented symptomatic postmeal hypoglycemia	9. Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic postmeal hypoglycemia within 1 and 2 hours after start of a meal from Week 12 through Week 26, Week 0 through Week 26, Week 26 through Week 52, and Week 0 through Week 52
10. To compare LY900014, LY900014+20, and insulin lispro with respect to the incidence and rate of documented symptomatic hypoglycemia	10. Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with events) of documented symptomatic hypoglycemic events from Week 12 through Week 26, Week 0 through Week 26, Week 26 through Week 52, and Week 0 through Week 52
11. To compare LY900014, LY900014+20, and insulin lispro with respect to 1,5-AG	11. Change from baseline 1,5-AG values at Week 26 and Week 52
12. To compare LY900014, LY900014+20, and insulin lispro with respect to 10-point SMBG profiles	12. Change from baseline 10-point SMBG values at Week 26 and Week 52
13. To compare LY900014 , LY900014+20, and insulin lispro with respect to total, basal, and prandial insulin dose	13. Change from baseline in total, basal and prandial insulin doses and prandial/total insulin dose ratios at Week 26 and Week 52
14. To compare LY900014, LY900014+20, and insulin lispro with respect to diabetes treatment satisfaction as measured by the ITSQ	14. Change from baseline in ITSQ regimen inconvenience and lifestyle flexibility domain scores at Week 26 and Week 52
15. To compare LY900014, LY900014+20, and insulin lispro with respect to the proportion of patients achieving HbA1c targets	15. The proportion of patients with HbA1c <7% and ≤6.5% at Week 26 and Week 52
16. To compare the glycemic control of LY900014 and insulin lispro	16. Actual and change from baseline to Week 52 in HbA1c
Tertiary/Exploratory Objectives	
17. To compare the safety of LY900014, LY900014+20, and insulin lispro	17. Adverse events, vital signs, chemistry, and hematology laboratory measures
18. To compare the incidence of treatment-emergent positive anti-insulin lispro antibodies for LY900014, LY900014+20, and insulin lispro	18. Incidence of treatment-emergent positive anti-insulin lispro antibodies

Objectives and Endpoints

Objectives	Endpoints
Tertiary/Exploratory Objectives (continued)	
21. To compare LY900014, LY900014+20, and insulin lispro with respect to changes in body weight	21. Change in weight (kg) from baseline to Week 26 and Week 52
22. To compare LY900014, LY900014+20, and insulin lispro with respect to the proportion of patients achieving improvement from baseline in HbA1c targets	22. The proportions of patients with shifts in HbA1c to <8% and ≤9%, and >9% from baseline to Week 26 and Week 52
23. To compare LY900014, LY900014+20, and insulin lispro with respect to glycemic variability	23. Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 10-point SMBG profiles

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; CCI [redacted] HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire; MMTT = mixed-meal tolerance test; NIM = noninferiority margin; PPG = postprandial glucose; SMBG = self-monitored blood glucose; T1D = type 1 diabetes mellitus; CCI [redacted]

5. Study Design

5.1. Summary of Study Design

Study ITRM is a Phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter 3-treatment group, parallel, active-controlled study in patients with type 1 diabetes mellitus (T1D) currently using a multiple daily injections regimen. For patients in the 2 double-blind treatment groups, the study includes a 1-week screening period and an 8-week lead-in period followed by a 52-week treatment period and a 4-week safety follow-up period. For patients in the open-label treatment group who are not in Japan, the treatment period will end after 26 weeks, which will be followed by a 4-week safety follow-up period. Open-label treatment group patients in Japan will follow the same schedule as the double-blind treatment groups. Figure 5.1 illustrates the study design.

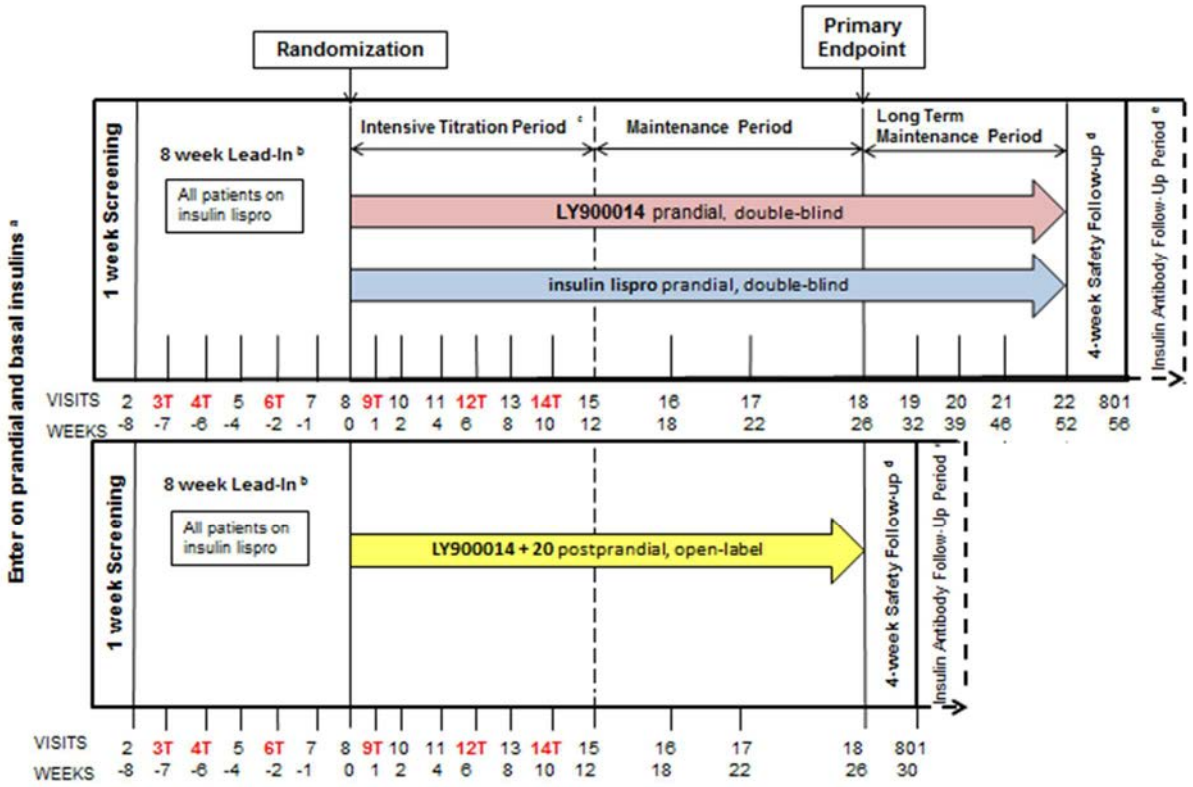
All patients who complete the 4-week safety follow-up visit (Visit 801) and have treatment-emergent anti-insulin lispro antibodies response that have not returned to the pre-specified baseline range (Visit 2) will be asked to participate in follow-up to monitor insulin lispro antibody levels for up to 26 weeks after Visit 801. The follow-up consists of Visits 802 and 803.

5.2. Determination of Sample Size

Assuming a noninferiority margin (NIM) of 0.4%, no true difference between treatment arms, and a standard deviation (SD) of 1.1%, approximately 371 completers in each double-blind treatment group will provide at least 99% power to show noninferiority between LY900014 and insulin lispro in change from baseline to 26 weeks in hemoglobin A1c (HbA1c) using the upper limit of a 2-sided 95% confidence interval (CI) (LY900014 – insulin lispro). Assuming a 15% dropout rate for 26 weeks, 4:4:3 randomization ratio (LY900014, insulin lispro, and LY900014+20), approximately 1199 patients will need to be randomized. This sample size also has 95% power to show noninferiority between LY900014 and insulin lispro using a 0.3% NIM at 26 weeks.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind or open-label treatment at Visit 8. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Patients will be randomized to double-blind LY900014, double-blind insulin lispro, or open-label LY900014+20 in a 4:4:3 ratio. Stratification will be by country, HbA1c stratum (≤7.5%, >7.5% at Visit 7), type of basal insulin during the lead-in period (glargine U-100 or degludec U-100), and prandial insulin dosing plan at randomization (carbohydrate counting, pattern adjustment).



Abbreviation: T = telephone visit.

a At Visit 2, patients on insulin glulisine or insulin aspart will be transferred to insulin lispro. The patients' basal insulin regimen will be switched to insulin glargine U-100 (once or twice daily) or to insulin degludec U-100 once daily. At Visit 8, patients will be randomized to either premeal insulin lispro, premeal LY900014, or LY900014+20 and continue their basal insulin regimen.

b Titrate basal insulin.

c Titrate prandial insulin (insulin lispro or LY900014).

d Patients will discontinue study insulins at Week 26 for the LY900014+20 open-label treatment group or Week 52 for the 2 blinded treatment groups.

e Eligible patients will have visits at approximately 3-month intervals for up to 26 weeks after Visit 801 for follow-up of insulin lispro antibody levels.

Figure 5.1. Illustration of study design.

6. A Priori Statistical Methods

6.1. General Considerations

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

Statistical analyses for the continuous glucose monitoring (CGM) addendum are provided in a separate SAP. Statistical analyses for Japan are described in Appendix 2. Statistical analyses for the Maximum Extended Enrollment (MEE) Addendum are described in Appendix 3.

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

Table 6.1. Patient Populations

Population	Description
Entered	All patients who give informed consent.
Enrolled	All patients who receive at least 1 dose of open-label insulin lispro in the 8-week lead-in period.
Randomized	All patients who are randomly assigned to study treatment at Visit 8. 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 investigational product (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.

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

The primary analysis is for the treatment period through Week 26. The primary endpoint is the HbA1c measurement obtained at Week 26 (Visit 18). The measurement obtained at Week 52 (Visit 22) will be a secondary endpoint.

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

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

- Lead-in Period – Visits 2-8
- 26-Week Treatment Period – from randomization to Week 26 prior to discontinuation of IP and from randomization to Week 26 (including all data regardless of IP use) – all treatment groups
- 26-Week Treatment Period and Safety Follow-Up Visit – from randomization to Visit 801 (including all data regardless of IP) – LY900014+20 treatment group excluding patients from Japan
- 52-Week Treatment Period - from randomization to Week 52 prior to discontinuation of IP and from randomization to Week 52 (including all data regardless of IP use) – double-blind treatment groups
- 52-Week Treatment Period and Safety Follow-Up Visit – from randomization to Visit 801 (including all data regardless of IP use) – double-blind treatment groups.

Patients randomly assigned to the LY900014+20 treatment group in Japan will remain in the study until Week 52 and subsequently will have the Safety Follow-Up Visit only after Week 52 for patients who complete the study.

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

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

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

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-squares (LS) means and standard errors derived from the analysis models will also be displayed. 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 Systeme International (SI) units will be presented. Therefore, both % and mmol/mol will be presented for HbA1c and both mg/dL and mmol/L will be presented for glucose measurements.

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

Table 6.2. Baseline and Postbaseline Definitions and Patient Population by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observations	Postbaseline Observations
Lead-In Period			
TEAEs	All Enrolled Patients	Prior to first dose of open-label insulin lispro (or Visit 2 date if the dose date is missing)	The entire lead-in period after first dose of open-label insulin lispro and prior to the first dose of IP (or Visit 8 date if the dose date is missing)
Basal, prandial, and total insulin doses, and prandial/total insulin dose ratio	All Randomized Patients	Visit 2	Visits 3–8 prior to initiation of IP
Weight MMRM and ANCOVA	All Randomized Patients	Last of Visits 1-2	Visits 3–8 AND Last of Visits 3-8
26-Week Treatment Period (including Safety Follow-Up Visit where applicable)			
HbA1c MMRM and ANCOVA (efficacy estimand)	All Randomized Patients with a baseline and at least 1 postbaseline observation while on IP	Last of Visits 7-8	Visits 11, 13, 15, and 18 prior to discontinuation of IP AND Last of Visits 9-18 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	Postbaseline Observations
HbA1c ANCOVA (ITT estimand)	All Randomized Patients with a baseline and at least 1 postbaseline observation	Last of Visits 7-8	Visit 18 regardless of IP use, with imputation for patients who discontinue the study prior to Visit 18
HbA1c categorical analyses longitudinal logistic regression and LOCF logistic regression	All Randomized Patients with a baseline and at least 1 postbaseline observation while on IP	Last of Visits 7-8	Visits 11, 13, 15, and 18 prior to discontinuation of IP AND Last of Visits 9-18 prior to discontinuation of IP
1-hr and 2-hr PPG and other MMTT variables (efficacy estimand)	All Randomized Patients with a postbaseline observation while on IP	Visit 8 prior to initiation of IP	Visit 18 prior to discontinuation of IP
1-hr and 2-hr PPG and other MMTT variables (ITT estimand)	All Randomized Patients with a postbaseline observation	Visit 8 prior to initiation of IP	Visit 18 regardless of IP use
10-point SMBG, basal, prandial, and total insulin doses, prandial/total insulin dose ratio	All Randomized Patients with a baseline and at least one postbaseline observation	Visit 8 prior to initiation of IP	Visits 11, 13, 15, and 18 prior to discontinuation of IP AND Last of Visits 9 to 18 prior to discontinuation of IP
1,5-AG	All Randomized Patients with a baseline and at least 1 postbaseline observation	Visit 8 prior to initiation of IP	Visits 11, 15, and 18 prior to discontinuation of IP AND Last of Visits 9-18 prior to discontinuation of IP
Health outcomes: ITSQ, CCI [redacted]	All Randomized Patients with a baseline and a postbaseline observation	Last of Visits 1-8	Last of Visits 9-18 prior to discontinuation of IP
Safety Laboratory Tests (chemistry, hematology, lipids) – continuous analysis	All Patients in the Safety Population with a baseline and a postbaseline observation	Last of Visits 1-8	Visit 18 (planned) AND Last of Visits 9-18 (planned including early discontinuation), regardless of IP use
Safety Laboratory Tests (chemistry, hematology, lipids) – categorical analysis	All Patients in the Safety Population with a normal baseline (with respect to the direction being analyzed) and a postbaseline observation	Visits 1 -8 (including unplanned tests)	Visits 9 to 18 (including unplanned tests), regardless of IP use

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

Study Period/Analysis	Patient Population	Baseline Observations	Postbaseline Observations
TEAEs	Safety Population	Prior to first dose of randomized IP (or Visit 8 date if missing) and after the first dose of open-label insulin lispro (or Visit 2 date if missing)	From first dose of randomized IP to last dose of randomized IP AND From first dose of randomized IP to Visit 18 or from first dose of randomized IP to Visit 801 (for LY900014+20 treatment group)
Hypoglycemia events	Safety Population	All Visits 2-8	All Visits 9-18 prior to discontinuation of IP
Weight and vital signs	All Patients in the Safety Population with a baseline and a postbaseline observation	Last of Visits 2-8	Visits 9-18 prior to discontinuation of IP AND Visits 9-18 regardless of IP use or Visits 9-801 for LY900014+20 treatment group
Anti-insulin lispro antibody	Safety Population	Visit 2	Visits 3-18 AND Visits 3-801 (for LY900014+20 treatment group), regardless of IP use
52-Week Treatment Period (including Safety Follow-Up Visit where applicable)			
HbA1c	All Randomized Patients in the Double-Blind Treatment Groups	Last of Visits 7-8	Visits 11, 13, 15, 18, 20, and 22 prior to discontinuation of IP AND Last of Visits 9-22 prior to discontinuation of IP
10-point SMBG, basal, prandial, and total insulin doses, prandial/total insulin dose ratio	All Randomized Patients in the Double-Blind Treatment Groups	Visit 8 prior to initiation of IP	Visits 11, 13, 15, 18, 20, and 22 prior to discontinuation of IP AND Last of Visits 9-22 prior to discontinuation of IP
1,5-AG	All Randomized Patients in the Double-Blind Treatment Groups	Visit 8 prior to initiation of IP	Visits 11, 15, 18, 20, and 22 prior to discontinuation of IP AND Last of Visits 9-22 prior to discontinuation of IP
Health outcomes: ITSQ[CCI] [redacted]	All Randomized Patients in the Double-Blind Treatment Groups	Last of Visits 1-8	Last of Visits 9-22 prior to discontinuation of IP
Safety Laboratory Tests (chemistry, hematology, lipids) – continuous analysis	All Double-Blind Patients in the Safety Population with a baseline and a postbaseline observation	Last of Visits 1-8	Visit 22 (planned) AND Last of Visits 9-22 (planned including early discontinuation), regardless of IP use

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

Study Period/Analysis	Patient Population	Baseline Observations	Postbaseline Observations
Safety Laboratory Tests (chemistry, hematology, lipids) – categorical analysis	All Double-Blind Patients in the Safety Population with a normal baseline (with respect to the direction being analyzed) and a postbaseline observation	Visits 1-8 (including unplanned tests)	Visits 9-22 (including unplanned tests) regardless of IP use.
TEAEs	All Double-Blind Patients in the Safety Population	Prior to first dose of randomized IP (or Visit 8 date if the dose date is missing) and after the first dose of open-label insulin lispro (or Visit 2 date if the dose date is missing)	From first dose of randomized IP to last dose of randomized IP AND From first dose of randomized IP to Visit 801
Hypoglycemia events	All Double-Blind Patients in the Safety Population	Visits 2-8	Visits 9-22 prior to discontinuation of IP
Weight and vital signs	All Double-Blind Patients in the Safety Population	Last of Visits 2-8	Visits 9-22 prior to discontinuation of IP AND Visits 9-801 regardless of IP use
Anti-insulin lispro antibody	All Double-Blind Patients in the Safety Population	Visit 2	Visits 3-801 regardless of IP use

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; ANCOVA = analysis of covariance; CCI [redacted]; HbA1c = hemoglobin A1c; IP = investigational product; ITSQ = Insulin Treatment Satisfaction Questionnaire; ITT = intention-to-treat; LOCF = last-observation-carried forward; MMTT = mixed meal tolerance test; MMRM = mixed-effect model repeated measures; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event; CCI [redacted]

6.2. Adjustments for Covariates

Stratification factors of this study include country, HbA1c stratum (≤7.5%, >7.5%), type of basal insulin during the lead-in period (glargine or degludec), and prandial insulin dosing plan (carbohydrate counting, pattern adjustment). Stratification factors will be entered into the IWRS for randomization and also collected in the database by electronic case report form (eCRF) or central laboratory. The analysis models for efficacy endpoints will use the stratification factors as collected in the database.

For continuous analyses of HbA1c, the stratification factor of HbA1c stratum will not be included. Instead, the continuous value of baseline (Visit 8) HbA1c will be included in the analysis models.

For analyses of the incidence and rate of hypoglycemia, the baseline hypoglycemia event rate with the same category of the dependent variable will be included as a covariate in the analysis models.

Other analyses will include the stratification factors as noted in Sections 6.11 and 6.12.

6.3. Handling of Dropouts or Missing Data

The analyses for the primary and multiplicity adjusted objectives will be performed for the intention-to-treat (ITT) estimand including all data collected through Week 26 regardless of IP use and the efficacy estimand including data collected prior to discontinuation of IP through Week 26.

For the FDA submission, the ITT estimand will be used. For the analysis of HbA1c, imputation of missing data will be performed as described in Section 6.11.1.

For non-FDA submissions and publications, the efficacy estimand will be used. Missing data will be addressed by using a mixed-effect model repeated measures (MMRM) analysis for continuous longitudinal variables. The MMRM model provides consistent estimator when data is missing at random. The model implicitly adjusts for missing data through a variance-covariance structure. An ANCOVA model will also be used to analyze continuous variables. Unless otherwise stated, missing endpoints will be imputed using the last-observation–carried forward (LOCF) approach, using only postbaseline data, in the ANCOVA model.

6.4. 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. Puerto Rico and the US are always pooled in the analysis, as Puerto Rico was considered part of the US during randomization. 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.

Given the different treatment period length between the Japan patients (52 weeks) and non-Japan patients (26 weeks) in the open-label arm, at the primary objective database lock (up to Week 26 for patients in the double-blind arms and up to Visit 801 for the non-Japan patients in the open-label arm), all analyses of the open-label arm involving data from Visit 801 will not include Japan patients.

To support the registrations for Taiwan, Russia, Korea, Mexico, and India, a MEE Addendum was developed to allow patient enrollment to continue in the study for these countries if they do not meet their minimum enrollment requirements for local registration. Separate analyses for these countries will be conducted to support their local registration (Appendix 3).

6.5. Multiple Comparisons/Multiplicity

A graphical approach for multiple comparisons will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the

multiplicity adjusted objectives given in Section 4. See Section 6.11.2 for the details of graphical testing scheme.

No multiplicity test adjustment will be made for other objectives.

6.6. Patient Disposition

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

Frequency counts and percentages of all randomized patients completing and discontinuing from the study and study treatment will be presented for each treatment group by period (0-26 Week, 0-52 Week, and 4-week safety follow-up period [Visit 801]). Reasons for discontinuation from the study and study treatment during the 26-week and 52-week treatment periods will be compared between treatment groups using Fisher's exact test. Reasons for discontinuation from the study at Visit 801 will be summarized by the randomized treatment groups.

At the primary objective database lock, a patient will be classified as a 26-week treatment completer if any of the following conditions holds:

- The patient has no study treatment discontinuation record whose visit number ≤18;
- The patient has a study treatment discontinuation record whose visit number = 18, and the number of days between the study treatment discontinuation date and the Visit 18 date is <10% of expected number of days between Visit 17 and Visit 18 = 10% * 28 days = 3 day.

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

Time to all-cause discontinuation (discontinuation for any reason) from the study and from study treatment will be compared between treatment groups for the 26-week Treatment Period and the 52-week Treatment Period. The Kaplan-Meier product limit method will be used to create survival curves and the log-rank test will be used for the treatment comparisons. Time to all-cause discontinuation is defined as the total number of days between the randomization date (Visit 8 date) and date of discontinuation plus 1. Patients who complete the treatment period will be treated as censored using the total number of days between the randomization date and the Visit 18 (or Visit 22) date plus 1. If sufficient numbers of patients discontinue the study because of an AE, similar analysis will be performed for time to discontinuation due to an AE.

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

Patient allocation by investigator, grouped by country, will be summarized indicating the number of patients who enter the study, the number of patients who participate in the lead-in period, the

number of patients who are randomized to study treatment, and the number of patients who discontinue the study.

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

6.7. Patient Characteristics

A summary table will be generated for patient characteristics at study entry using all randomized patients. The following variables will be included but not limited to: age, age groups (<40 and ≥40 years and 18 to 64, 65 to 85, and ≥85 years), sex, country, ethnicity, race, height, weight, body mass index (BMI), BMI groups (<25, ≥25 to <30, ≥30 kg/m^2). For continuous variables, the following statistics will be provided: mean, SD, minimum, maximum, and median, and treatment groups will be compared using an ANOVA model with a term of treatment. For categorical variables, summary statistics will include sample size, frequency and percentage, and treatment groups will be compared using Fisher's exact test or Pearson's chi-square test. A listing of patient characteristics at study entry will be provided.

A similar summary of diabetes characteristics will also be generated. The following variables will be included but not limited to: duration of diabetes, the type of prandial insulin at study entry (that is, screening), the type of basal insulin therapy at study entry (including whether given once daily [QD[or twice-daily [BID]) and during lead-in, prandial insulin dosing plan, personal continuous glucose monitoring (CGM)/flash glucose monitoring (FGM) use during the study, HbA1c at study entry and baseline, HbA1c stratum at baseline, and fasting serum glucose at Visit 2 and baseline (based on MMTT).

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) PT (without regard to SOC), and the number and percentage of patients with preexisting conditions will also be summarized by treatment group using MedDRA PT (without regard to SOC). Historical conditions are conditions that end prior to inform consent and preexisting conditions are conditions that are still ongoing at inform consent. Events will be ordered by decreasing frequency. No statistical comparisons between treatment groups will be performed.

6.8. Treatment Compliance

The prandial insulin dose times and meal times will be collected for assessing compliance of the timing of prandial insulin administration relative to meal time (premeal and postmeal). The difference between dose time and meal time will be calculated when both times are entered into the Electronic Clinical Outcomes Assessment (eCOA) device during the treatment period prior to discontinuation of IP for all randomized patients. Summary statistics will be presented for the difference between dose and meal times for each treatment group. The percentage of dose times within +/- 5 minutes of the protocol-specified dose timing (that is, -7 to +5 minutes for pre-meal

dosing and +15 to +25 minutes for postmeal dosing) will be summarized by treatment group. No statistical comparisons between treatment groups will be performed.

6.9. 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. Patients with more than one IPD from the same category, subcategory, and study specific term (description) will only be counted once per patient.

Table 6.3 lists the categories/subcategories of important protocol deviations, source of identification, and the method to identify each deviation.

Table 6.3. Description of Important Protocol Deviations

Category	Sub-categories	Description	Source	Methods of Identification
Informed Consent	Informed Consent Not Obtained		Mixed (monitoring and clinical database)	Applicable to main protocol and CGM addendum. Compare all assessment dates to ICD date (except those assessments that may occur before ICD, eg, disease assessments).
Informed Consent	Improper Consent		Non Programmable (monitoring)	Applicable to main protocol and CGM addendum. Failure to reconsent after an ICD amendment at first possible visit. Unauthorized personnel administered ICD. Patient signed incorrect version of ICD (and failure to reconsent using the correct version of ICD prior to first CGM visit for the CGM addendum). ICD was not dated. ICD was lost.
Informed Consent	Revoke Consent		Non Programmable (monitoring)	Applicable to main protocol and CGM addendum). Patient revoked ICD.
Eligibility	Inclusion/ Exclusion	Type of patient and disease characteristics	Mixed (monitoring and clinical database)	CRF Medical History, Diabetes Duration panel data to indicate diagnosis date of T1D per protocol <1 year prior to screening date, and Prior Diabetes Therapies / Basal Insulin / Bolus Insulin panel data to indicate start date for continuously using insulin <1 year prior to screening date. Also identified by CRA as captured in sCTMS. Entry Criteria #1.

Description of Important Protocol Deviations

Category	Sub-categories	Description	Source	Methods of Identification
Eligibility	Inclusion/ Exclusion	Age not in compliance with entry criteria	Mixed (monitoring and clinical database)	CRF data to indicate the age <18 yrs at Visit 1. Also identified by CRA as captured in sCTMS. Entry Criteria #2
Eligibility	Inclusion/ Exclusion	HbA1c not in compliance with entry criteria	Programmable (clinical database)	Central Laboratory data to indicate that entry HbA1c not compliant with entry criteria #5.
Eligibility	Inclusion/ Exclusion	Hematological conditions	Mixed (monitoring and clinical database)	CRF Pre-existing Conditions panel data using MedDRA terms that are considered as relevant hematological conditions by the CRP/CRS to indicate not compliant with entry criteria #25 Also identified by CRA as captured in sCTMS.
Eligibility	Inclusion/ Exclusion	Previous noninsulin antihyperglycemic medications	Mixed (monitoring and clinical database)	CRF Prior Diabetes Therapies / Concomitant Therapy panel data to indicate not compliant with entry criteria #32. Also identified by CRA as captured in sCTMS.
Eligibility	Inclusion/ Exclusion	Previous insulin therapy	Mixed (monitoring and clinical database)	CRF Prior Diabetes Therapies / Concomitant Therapy panel data to indicate not compliant with entry criteria #3, #4, #29, #30, #31. Also identified by CRA as captured in sCTMS.
Investigational Product	Treatment Assignment/ Randomization Error		Mixed (monitoring and clinical database)	IWRS data entry errors that impact patient stratification, for example, lab data indicated different strata from IWRS stratification report. Dispensing error: Patient was assigned to a treatment, but site gave a different treatment to the patient.
Investigational Product	Unblinding		Non Programmable (monitoring)	Any inadvertent unblinding affecting, patients, investigator, or sponsor.
Investigational Product	Patient Took Medication Not Fit for Use		Non Programmable (monitoring)	Study Drug not fit for use administered to patient.
Investigational Product	Other	Use of expired CT material	Non Programmable (monitoring)	Also identified by CRA as captured in sCTMS.

Description of Important Protocol Deviations

Category	Sub-categories	Description	Source	Methods of Identification
Study Procedures	Violation of Discontinuation Criteria		Mixed (monitoring and clinical database)	Patients not discontinued from treatment and/or study despite having met protocol specified discontinuation criteria. Also identified by CRA as captured in sCTMS Protocol Section 8.
Study Procedures	Excluded Conmeds		Mixed (monitoring and clinical database)	CRF Prior Diabetes Therapies / Concomitant Therapy panel data to indicate not compliant with entry criteria #28 and study-specific restriction on concomitant therapies Table ITRM.8 in the study protocol. Also identified by CRA as captured in sCTMS.
Study Procedures	Lab/Imaging Criteria	Missing HbA1c at baseline/at the primary endpoint	Mixed (monitoring and clinical database)	Central laboratory data to indicate that a). HbA1c is not collected at both Visit 7 and Visit 8 or b). HbA1c is not collected at the primary endpoint (only applicable to patients who completed the primary endpoint without early discontinuation from the study).
Study Procedures	Visit Schedule Criteria		Programmable (clinical database)	CRF Subject Visit panel data to indicate that 2 consecutive office visits are completely missing.
Study Procedures	Other	Electronic Clinical Outcomes Assessment (eCOA)	Programmable (clinical database)	Comparison of patient data from CRF and eCOA to identify randomized patients who have no ediary data entered.
Administrative/ Oversight	Suspected Misconduct		Non Programmable (monitoring)	Site staff sharing account details for systems (e IWRS, EDC or ePresentOnline). Suspected falsification of data.
Safety	Safety Mailings		Non Programmable (monitoring)	Lack of, significant delay in safety mailing review (significant delay defined as a delay of 90 days).
Safety	SAEs		Non Programmable (monitoring)	Failure to report an SAE within 24 hours of the investigator being made aware of the SAE. Failure to respond to SAE queries.

Description of Important Protocol Deviations

Category	Sub-categories	Description	Source	Methods of Identification
Safety	Other	Failure to report product complaint within 24 hours.	Non Programmable (monitoring)	Identified by CRA as captured in sCTMS.

Abbreviations: # = number of inclusion/exclusion criteria in protocols; CGM = continuous glucose monitoring; CRA = clinical research associate; CRF = clinical (case) report form; CRP = clinical research physician; CRS = clinical research scientist; CT = clinical trial; HbA1c = hemoglobin A1c; ICD = informed consent document; eCOA = Electronic Clinical Outcome Assessments; EDC = Electronic Data Capture; IWRS = interactive Web Response System; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; sCTMS = Simplicity Clinical Trial Management System; T1D = type 1 diabetes; yrs = years.

Furthermore, of the above listed important protocol deviations, the following may significantly impact the results of the primary objective:

- lack of informed consent
- have any hematological condition that may interfere with HbA1c measurement
- missing HbA1c at both Visit 7 and Visit 8, or missing HbA1c at the primary endpoint.

Patients with one or more such deviations will be excluded from the Per Protocol (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 an IPD is identified by both methods, only the site monitoring IPD will be presented.

6.10. Concomitant and Prior Therapy

Concomitant medication will be summarized and compared between treatment groups using Fisher's exact test for the Randomized Population during the treatment periods (0 to 26 weeks, 0 to 52 weeks). The percentages of patients receiving each concomitant medication will be summarized by treatment using PT nested within Anatomical Therapeutic Chemical (ATC) Level 3 code. Medications will be ordered by decreasing frequency within ATC level. Concomitant medication used during the lead-in period will also be summarized for the Enrolled Population.

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

Total daily basal insulin and total daily prandial insulin doses for the day prior to Visit 2 will be entered into the eCRF. After visit 2, the daily basal doses and individual prandial insulin doses (that is, morning meal, midday meal, evening meal, bedtime/snack/other) will be entered into the eCOA device. At a given visit, total daily basal insulin dose to be used for analysis will be calculated as the mean of the total daily basal insulin doses on the 7 days prior to the visit date (or the days between the previous visit date and the current visit date if the number of days

between the 2 visit dates is <7). Similarly, the dose for each meal will be calculated as the mean of the doses on the 7 days prior to the visit date (or the days between the previous visit date and the current visit date, whichever smaller). Total daily prandial insulin dose to be used for analysis will be calculated as the sum of the individual meal insulin doses. If either total daily basal insulin dose or total daily prandial insulin dose is missing, total daily insulin dose and prandial/total insulin dose ratio will be set as missing for analysis.

The total daily basal insulin dose, total daily prandial insulin dose, total insulin dose, and the ratio of prandial insulin dose to total insulin dose during the lead-in period will be summarized by visit for the Randomized Population. The actual and change from Visit 2 values will be compared between treatment groups using an MMRM model including the corresponding dose at Visit 2, treatment, strata (pooled country, type of basal insulin, prandial insulin dosing plan, and HbA1c stratum), visit, treatment-by-visit interaction in the model as fixed factors and patient as a random factor. Doses will be summarized in U and U/kg. Basal insulin dose will be summarized independently for glargine and degludec as well as combined.

6.11. Efficacy Analyses

6.11.1. Primary Outcome and Methodology

The primary objective of this study (H1) is to test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control (NIM=0.4% for HbA1c) in patients with T1D, when administered as prandial insulin (0-2 minutes prior to the meal), 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, the primary analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand that will include all data collected from randomization through Week 26, regardless of IP use. The reference will be all observed data from the randomized patients in the same treatment group who discontinue IP and complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro 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 prandial insulin dosing plan) as fixed effects and baseline HbA1c as a covariate.

If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis such that the model cannot converge or the number of records without missing data is less than the number of records with missing data, the missing HbA1c measurement at Week 26 will be imputed by the patient-level observed baseline value plus a noise assuming a washout of any potential treatment effect (that is, “return to baseline”). The noise follows a normal distribution with the variability estimated from the “washout HbA1c data,” which will be derived by subtracting the corresponding treatment mean at Week 26 from individual non-missing HbA1c values at Week 26.

For non-FDA submissions and publications, the primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro at Week 26 (Visit 18) from the MMRM analysis of change from baseline in HbA1c including data collected from all randomized patients prior to discontinuation of IP through Week 26 (efficacy estimand). The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment, strata (pooled country, type of basal insulin, and prandial insulin dosing plan), 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 insulin lispro 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 insulin lispro 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. The ANCOVA and MMRM analyses will include data from all 3 treatment groups; however, the contrasts between LY900014+20 and insulin lispro and between LY900014 and LY900014+20 are not part of the primary efficacy comparisons.

6.11.2. Analyses of Multiplicity Adjusted Objectives

A graphical approach for multiple comparisons (Bretz et al. 2011) will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the following multiplicity adjusted objectives: superiority of LY900014 compared with insulin lispro for (H2) 1-hour postprandial plasma glucose (PPG) excursion at the study primary endpoint, (H3) 2-hour PPG excursion at the study primary endpoint, and (H4) change from baseline to the study primary endpoint in HbA1c, and (H5) noninferiority of LY900014+20 to insulin lispro in change from baseline to the study primary endpoint in HbA1c. Analyses will be performed for both the efficacy estimand and ITT estimand.

The graphical testing scheme for this study is displayed in Figure 6.1. All the hypotheses are connected by lines with arrowheads indicating the directions of testing paths. The initial allocation of study total alpha for each hypothesis is located within the same node of the

hypothesis. In this study, the study total alpha level (0.05) will be all used for the primary objective (H1) in the initial step. The alpha level will all be allocated to H5 if H1 is successfully demonstrated. Then, the study total alpha level (0.05) will be allocated to other objectives according to the values of transition weights shown above the connecting lines in the figure. If 1 of the remaining objectives is successfully demonstrated with the given alpha level, its alpha will be allocated to the rest of objectives by the transition weights in the paths. The iterative test procedure continues until none of the remaining objectives can be demonstrated with their preserved alphas or all objectives are demonstrated successful.

An ANCOVA model with strata (pooled country, type of basal insulin, prandial insulin dosing plan, and HbA1c stratum) and treatment as fixed effects and baseline as a covariate will be used to analyze the 1-hour and 2-hour PPG excursions for both the efficacy (data collected prior to discontinuation of IP) and ITT (all data collected regardless of IP use) estimands. However, if the percentage of the patients with MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead. The ANCOVA analysis will include data from all 3 treatment groups; however, the contrasts between LY900014+20 and insulin lispro and between LY900014 and LY900014+20 are not part of the multiplicity adjusted comparisons.

The superiority testing on change from baseline to the study primary endpoint in HbA1c will be assessed by the same analysis used for the primary objective. The noninferiority of LY900014+20 to insulin lispro in the change from baseline in HbA1c at Week 26 will also be analyzed by the same analysis. The analyses for the ITT and efficacy estimands are described in Section 6.11.1. If the p-value is less than the alpha level allocated by the graphical approach, the superiority of LY900014 to insulin lispro or the noninferiority of LY900014+20 to insulin lispro will be achieved.

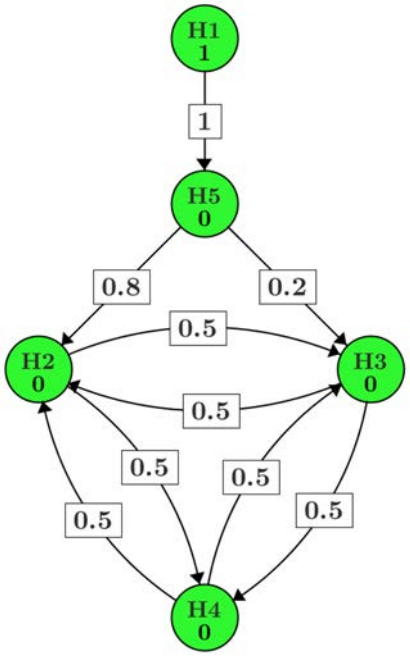


Figure 6.1. Testing scheme for primary and multiplicity adjusted objectives.

6.11.3. 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 prandial insulin dosing plan) and treatment as fixed effects and baseline as a covariate. Missing endpoints will be imputed using the LOCF approach using postbaseline data only.

6.11.4. Sensitivity Analyses for Missing Data

A missing-not-at-random (MNAR)-based analysis will be performed for both the efficacy and ITT estimands to assess sensitivity to departures from the missing-at-random (MAR) assumption by repeatedly adjusting the imputations of missing data to provide a progressively more severe 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. Imputation under the noninferiority null method (where delta equals the NIM) will be included as a special case of the progressive stress test.

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

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

6.11.5. Other Secondary Efficacy Analyses

The analyses described in Section 6.11.5 to Section 6.11.7 will include data collected from all randomized patients prior to discontinuation of IP (efficacy estimand). 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. For the following secondary efficacy endpoints, an MMRM model similar to that for the primary outcome with an additional term of HbA1c stratum (≤7.5%, >7.5%) will be used:

- actual and change from baseline 1,5-AG values
- actual and change from baseline 10-point SMBG values (fasting, 1 hour post morning meal, 2 hours post morning meal, pre midday meal, 1 hour post midday meal, 2 hours post midday meal, pre evening meal, 1 hour post evening meal, 2 hours post evening meal, and bedtime)
- actual and change from baseline in total, basal, and prandial insulin doses and prandial/total insulin dose ratios

Three 10-point SMBG profiles are expected to be collected during the 2 weeks prior to specified visits. Valid SMBG profiles will be used for analysis, defined as having non-missing values at ≥6 time points among the 10 pre-specified time points and being collected 2 weeks prior to the given visit. For each time point, the average of the corresponding SMBG values from the valid SMBG profiles will be used for analysis.

The following endpoints, collected from the MMTT, will be analyzed using the ANCOVA model with strata (pooled country, type of basal insulin, prandial insulin dosing plan, and HbA1c stratum) and treatment as fixed effects and baseline as a covariate:

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

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

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

patients with HbA1c <7.0% and ≤6.5% at Week 26 (Visit 18), imputed using LOCF, will be compared using a logistic regression model with terms for treatment and baseline HbA1c value.

6.11.6. Secondary Health Outcomes Analyses

For the Insulin Treatment Satisfaction Questionnaire (ITSQ), the change from baseline to LOCF endpoint while on treatment in each domain transformed score[redacted] and overall transformed score will be analyzed using the ANCOVA model with strata (pooled country, type of basal insulin, prandial insulin dosing plan, and HbA1c stratum), and treatment as fixed effects and baseline as a covariate.

All above analyses will be conducted using data from all 3 treatment groups for the treatment period up to the primary endpoint (Week 26). The analyses will be repeated with additional data collected after the primary endpoint up to Week 52 using the data from the 2 double-blind treatment groups.

6.11.7. Analyses of Exploratory Objectives

[redacted]

Within-day and between-day glycemic variability measured by the standard deviation (SD) and the coefficient of variation (CV) of 10-point SMBG profiles will also be analyzed by MMRM model specified in Section 6.11.5. At a given visit, the CV and SD on each day with a valid SMBG profile will be calculated using all the glucose values within that day, then the average values of these CVs and SDs will be used as the within-day CV and SD at that visit in analysis. At a given visit, the CV and SD at each of the 10 pre-specified SMBG time points will be calculated using the corresponding glucose values of the valid SMBG profiles, then the average values of these CVs and SDs will be used as the between-day CV and SD at that visit in analysis.

The above analyses will be conducted separately for the treatment periods of 0 to 26 weeks and 0 to 52 weeks. The first period will use data from all treatment groups while the second period will only use data from the double-blind treatment groups.

Table 6.4 lists additional variables for potential exploratory analyses.

Table 6.4. Additional Exploratory Efficacy Variables

Variable Description	Derivation	Statistical Method
Incremental areas under the serum glucose concentration-time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after the meal in MMTT.	iAUC+: the total area under the serum glucose curve but above the glucose level at time 0 when the meal starts for the MMTT within the specific time frame. The area will be calculated by trapezoids rule.	ANCOVA
Area under/above the serum glucose concentration time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after the meal in MMTT.	• AUC: Total area under the serum glucose curve calculated by trapezoids area within the specific time frame • $AUC_{>180}$: Total area under the serum glucose curve but above the 18 0mg/dL level within the specific time frame • $AOC_{\leq 70}$: Total area above the serum glucose curve but below the 70 mg/dL level within the specific time frame.	ANCOVA
Glucose variability during MMTT	• The CV of all serum glucose values collected during the MMTT • The SD of all serum glucose values collected during the MMTT.	ANCOVA
1-hour and 2-hour PPG excursions and daily mean by 10-point SMBG profile	• The difference in means between 1-hour PPG and fasting PG at the same visit • The difference in means between 2-hour PPG and fasting PG at the same visit • The average of daily means at the same visit	MMRM
Incidence of HbA1c ≤6.5% and <7.0% without severe hypoglycemia	• Binary indicator with 1 indicating HbA1c ≤6.5% at Week 26 and no severe hypoglycemia during 0-26 weeks of treatment • Binary indicator with 1 indicating HbA1c <7% at Week 26 and no severe hypoglycemia during 0-26 weeks of treatment.	Logistic regression

Abbreviations: ANCOVA = analysis of covariance; AOC = area over the curve; AUC = area under the curve; CV = coefficient of variation; iAUC = incremental area under the curve; HbA1c = hemoglobin A1c; MMRM = mixed-meal tolerance test; MMTT = mixed-meal tolerance test; PG = plasma glucose; PPG = postprandial glucose; SD = standard deviation; SMBG = self-monitored blood glucose.

6.12. Safety Analyses

Safety measures will include AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro. Refer to Table 6.1 and Table 6.2 for the analysis population and the baseline definition used in the analysis of a safety measurement for a specific study period.

6.12.1. Extent of Exposure

Duration of exposure to IP will be summarized. The following summary statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (that is, total patient-years of exposure). The number and proportion of patients falling into the following different exposure categories will also be summarized: <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). For the double-blind treatment groups, 2 additional exposure categories: ≥6 and <12 months (≥180 days and <360 days) and ≥12 months (≥360 days), will be summarized.

Patients who complete the study treatment period are required to complete a safety follow-up visit without study drug; and patients who discontinue the IP prematurely are encouraged to remain in the study without study drug. The days on study after discontinuing IP, and the days on study from date of first study drug to the last study visit date up to Visit 801 will also be summarized.

6.12.2. Adverse Events

Analyses of AEs will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data prior to discontinuation of IP. The second set of analyses will include all data in the corresponding analysis period regardless of IP use.

Events that are newly reported after the first dose of prandial insulin provided as study drug (that is, open-label insulin lispro used during the lead-in period or IP used during the treatment period) or reported to worsen in severity from baseline (defined in Table 6.2 for a specific study period) will be considered 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 bolus insulin provided by this study, the case report form (CRF)-collected flag will be used to determine whether the event started or worsened post-treatment.

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

The number and percentage of patients with TEAEs will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. As an additional table, the percentages of patients with TEAEs will be summarized by treatment using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency. 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 (without regard to SOC) and data collected prior to 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 in 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 an SAE, including deaths and SAEs temporally associated or preceding deaths, will be summarized by treatment group using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency within SOC. 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) using all data regardless of IP use. 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) using data prior to discontinuation of IP. 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.

Table 6.5 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 discontinuation of IP will be included.

Table 6.5. Treatment-Emergent Adverse Event Analysis Periods

Analysis Period	Analysis Population	Analysis	IP USE	Treatment
Lead-in Period	All enrolled patients	AE overview; TEAE by PT, SAE, discontinuation from study due to AE	N/A	Open-label insulin lispro
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; discontinuation from IP due to AE	Yes	LY900014, insulin lispro, LY900014+20
Treatment Period (0-26 Weeks)	All patients in safety population	AE overview; TEAE by SOC; common TEAE; SAE; discontinuation from study due to AE; other notable AEs	All data regardless of IP use	LY900014, insulin lispro, LY900014+20
Treatment Period (0-52 Weeks)	All patients with double-blind treatment in safety population	AE overview; TEAE by SOC and by PT; common TEAE; TEAEs by maximum severity; SAE; discontinuation from IP due to AE	Yes	LY900014, insulin lispro
Week 0 – 26 + Visit 801	All patients with open-label treatment in safety population (excluding Japan)	AE overview; TEAE by SOC; common TEAE; SAE; other notable AEs	All data regardless of IP use	LY900014+20
Week 0 – 52 + Visit 801	All patients with double-blind treatment in safety population	AE overview; TEAE by SOC; common TEAE; SAE; discontinuation from study due to AE; other notable AEs	All data regardless of IP use	LY900014, insulin lispro

Abbreviations: AE = adverse event; IP = investigational product; N/A = not applicable/available; PT = Preferred Term; SAE = Serious Adverse Event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

6.12.3. 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 ID, investigator ID, patient ID, treatment group, baseline age, sex, associated AE, first and last dose date for open label insulin lispro and randomized IP, and the event date.

6.12.4. Hypoglycemic Events and Other Adverse Events

The analysis plans for the following adverse events are discussed in Section 6.12.4.1 through Section 6.12.4.4:

- hypoglycemic events
- systemic hypersensitivity reaction
- injection site reaction

- hepatobiliary events

These AE analyses will be similar to the TEAE analyses. Refer to Table 6.5 for the requirement of analysis data for a specific analysis period.

6.12.4.1. Hypoglycemic Events

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

The following types of hypoglycemia events will be derived in the analysis data sets: documented hypoglycemia, severe hypoglycemia, nocturnal hypoglycemia (documented and occurring between bedtime and waking), probable symptomatic hypoglycemia, and overall hypoglycemia. Only severe hypoglycemia will be collected as AEs and all episodes of severe hypoglycemia will be considered as SAEs. Documented hypoglycemia (including documented symptomatic hypoglycemia, documented asymptomatic hypoglycemia and documented unspecified hypoglycemia) will be based on blood glucose (BG) ≤70 mg/dL. In addition, documented clinically significant hypoglycemia with similar criterion as above documented hypoglycemia except for the threshold of BG <54 mg/dL will be summarized. Hypoglycemia identified by CGM for patients in the CGM Addendum will not be included in these analyses.

Table 6.6 provides detailed statistical methods for each endpoint related to hypoglycemia. For these analyses, hypoglycemia events prior to discontinuation of IP will be summarized. For the analysis period prior to Week 26, the analysis data will include data from all 3 treatment groups. For the analysis period after Week 26, the analysis data will only include data from the 2 double-blind treatment groups. Additional analyses for other types of hypoglycemic events not mentioned in the table and for the post-treatment period may be conducted as needed.

The incidence and number of episodes of hypoglycemia (regardless of the type of hypoglycemia event) during the MMTT will be summarized by treatment and time relative to the meal (≤0.5, ≤1, ≤2, ≤4, >1 to ≤2 and >2 to ≤4 hours after start of the meal) and analyzed by Fisher's exact test.

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 6.6. Summary of Analyses for Endpoints Related to Hypoglycemia

Endpoint	Analysis Period	Statistical Method
Rate of hypoglycemic events (per patient per 30 days / year) All Documented[a] Nocturnal[a] Documented Symptomatic[a] Overall Non-Nocturnal (or Daytime) (Documented and between waking and bedtime)[a] Probable Symptomatic	0-4, 0-12, 0-26, 4-8, 8-12, 12-26, 26-52, 0-52 weeks	Negative binomial regression with treatment, and baseline hypoglycemia event rate with the same category of the dependent variable as covariates, log (exposure/30/365.25 days) as the offset in the model.
Incidence of hypoglycemic events All Documented[a] Nocturnal[a] Documented Symptomatic[a] Overall Non-Nocturnal (or Daytime) (Documented and between waking and bedtime)[a] Probable Symptomatic	0-4, 0-12, 0-26, 4-8, 8-12, 12-26, 26-52, 0-52 weeks	Logistic regression with treatment, baseline hypoglycemia event rate with the same category of the dependent variable as covariates.
Rate of postmeal hypoglycemic events (per patient per 30 days / year) for all 3 main meals Documented Symptomatic[a] Documented Asymptomatic[a]	≤0.5, ≤1, ≤2, ≤4, >1 to ≤2 and >2 to ≤4 hours after start of a meal within 0-12, 12-26, 0-26, 26-52, 0-52 weeks	Negative binomial regression with treatment, baseline postmeal hypoglycemia event rate with the same category of the dependent variable as covariates, log (exposure/30/365.25 days) as the offset in the model.
Incidence of postmeal hypoglycemic events for all 3 main meals Documented Symptomatic[a] Documented Asymptomatic[a]	≤0.5, ≤1, ≤2, ≤4, >1 to ≤2 and >2 to ≤4 hours after start of a meal within 0-12,12-26, 0-26, 26-52, 0-52 weeks	Logistic regression with treatment, baseline postmeal hypoglycemia event rate with the same category of the dependent variable as covariates.
Rate of severe hypoglycemic events (per patient per year / 100 years)	0-12, 0-26, 12-26, 26-52, 0-52 weeks	Exposure adjusted rate per year / 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.

Summary of Analyses for Endpoints Related to Hypoglycemia

Endpoint	Analysis Period	Statistical Method
Incidence of severe hypoglycemic events	0-12, 0-26, 12-26, 26-52, 0-52 weeks	Proportion of patients with severe hypoglycemia will be reported. The treatment comparison will be based on a logistic regression model with treatment and baseline rate as a covariate.
Rate of postmeal severe hypoglycemic events (per patient per year / 100 years) for all 3 main meals	0-12,12-26, 0-26, 26-52, 0-52 weeks	Due to limit data for the rare event, only summary statistics will be provided by treatment. No statistical comparison will be conducted.
Incidence of postmeal severe hypoglycemic events for all 3 main meals	0-12, 12-26, 0-26, 26-52, 0-52 weeks	Fisher exact test will be used for treatment comparison.

[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, except for postmeal hypoglycemia for which only the threshold of ≤70 mg/dL will be applied.

6.12.4.2. 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 Standardised MedDRA Query (SMQ) will be used to identify potential systemic hypersensitivity reactions from all TEAEs:

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

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

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

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

6.12.4.3. 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 reaction 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 were collected through the eCRF, and will be summarized for each treatment. There will be no statistical comparison between treatments.

6.12.4.4. Hepatobiliary Events

6.12.4.4.1. 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.

6.12.4.4.2. Liver Enzyme and Bilirubin 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 tests) will be summarized for patients who have both a baseline and at least 1 postbaseline result, and compared between treatment groups by using ANCOVA model with the term of treatment and baseline value of the response variable. All analyses will be provided in both SI and CN units.

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

The analyses for Week 52 will be similar to that described above using data for the 2 double-blind treatment groups.

6.12.4.4.3. 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 to 26, 0 to 52 weeks) will be summarized between treatment groups:

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

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

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

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

6.12.5. 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 analyses for Week 52 will be similar to that described above using data for the 2 double-blind treatment groups.

The percentages of patients with treatment-emergent abnormal, high, or low laboratory results at any time during the treatment period (0 to 26, 0 to 52 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 analysis being performed will be included in the analysis for treatment-emergence.

Liver enzymes measures will not be included in the above analyses as different analyses will be used as described in Section 6.12.4.4.2 and Section 6.12.4.4.3.

6.12.6. Vital Signs and Other Physical Findings

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

The measurements during the treatment period (0 to 26, 0 to 52 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.

Weight during the lead-in period will also be analyzed by an MMRM model with Visit 2 value of the response variable, randomized treatment, visit, and treatment-by-visit interaction as fixed factors and patient as the random factor in all randomized patients.

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

Change from the minimum value during the baseline period to the minimum value during the treatment period (0 to 26, 0 to 52 weeks) for vital signs and physical characteristics will be summarized for patients who have both baseline and at least 1 postbaseline result. Baseline will be the minimum of nonmissing observations in the baseline period. The minimum value in the treatment period will be analyzed. Similarly, change from the maximum value during the baseline period to the maximum value during the treatment period (0 to 26, 0 to 52 weeks) for vital signs and physical characteristics will be summarized for patients who have both baseline

and at least 1 postbaseline result. Baseline will be the maximum of nonmissing observations in the baseline period. The maximum value in the treatment period will be analyzed.

The percentages of patients with treatment-emergent high or low vital signs and weight at any time during the treatment period (0 to 26, 0 to 52 weeks) or during the entire study including safety follow-up period will be summarized by treatment group (0 to 26: all 3 treatment groups; 0 to 52: only the 2 double-blind treatment groups) for patients who have both baseline and at least 1 postbaseline measurement. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time that meets the specified change criteria during the treatment period or during the entire study including safety follow-up period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time that meets the specified change criteria during the treatment period or during the entire study including safety follow-up period. Treatment comparison will be based on Fisher's exact test. Table 6.7 will be used to define the low and high limits and change thresholds.

Table 6.7. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

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

Abbreviations: BP = blood pressure.

6.12.7. Immunogenicity

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro for all enrolled patients since Visit 2 prior to the first dose of study-provided prandial insulin treatment. Therefore, the blood sample result at Visit 2 will be considered as the anti-insulin lispro level at baseline for this study.

Patients who complete the 4-week safety follow-up visit (Visit 801) and have treatment-emergent anti-insulin lispro antibodies that have not returned to prespecified baseline range (Visit 2) will be asked to participate in follow-up to monitor antibody levels. The assessment of immunogenicity will include analyses of treatment-emergent anti-insulin lispro antibody up to

Visit 801 and analyses of anti-insulin lispro antibody return to baseline during the insulin lispro antibody safety follow up period.

6.12.7.1. Treatment Emergent Anti-Insulin Lispro Antibody

The treatment-emergent anti-insulin lispro antibody (denoted as treatment-emergent antidrug antibody [TEADA] throughout this SAP) is based on the change from baseline (Visit 2) to postbaseline (post-Visit 2) in the anti-insulin lispro antibody level (percent binding). Treatment-emergent antidrug antibody can be sub-classified as either treatment-induced (not detected anti-insulin lispro antibody at baseline) or treatment-boosted (detected anti-insulin antibody at baseline):

- treatment-induced response: change from not detected anti-insulin lispro at baseline (Visit 2) to postbaseline detected anti-insulin lispro;
- treatment-boosted response: change from detected anti-insulin lispro at baseline (Visit 2) to postbaseline detected anti-insulin lispro antibody level (percent binding) at least 157% of the baseline value.

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

The number and percentage of patients with positive TEADA response during the treatment period of 0 to 26 weeks will be summarized by treatment group. For patients with positive TEADA response during the treatment period of 0 to 26 weeks, the number and percentage of patients with positive insulin cross-reactivity anytime during the treatment period of 0 to 26 weeks will also be summarized by treatment group. Treatment groups will be compared by Fisher's exact test.

The above summary of TEADA response will be repeated for the analysis period of Visit 2 to Visit 801. The 2 double-blind treatment groups and the open-label treatment group will be summarized separately due to different duration of treatment period. For patients with positive TEADA response, the number and percentage of patients not meeting the TEADA criteria at Visit 801 will also be summarized.

Both actual and change from baseline (Visit 2) for the anti-insulin lispro antibody level in percent binding will be summarized by scheduled visit prespecified in the protocol for patients with positive TEADA response during the treatment period of 0 to 26 weeks. The repeated measurement from Visit 2 to Visit 18 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 maximum percent binding during the treatment period of 0 to 26 weeks. A similar summary of antibody level in percent binding during the analysis period of Visit 2 to Visit 801 will be generated separately for the 2 double-blind treatment groups and the open-label treatment group.

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

Subgroup analysis for the following selected efficacy and safety variables will be performed by the TEADA status during the treatment period of 0 to 26 weeks:

- Use data prior to discontinuation of IP:
    - HbA1c and change from baseline in HbA1c
    - 1-hour and 2-hour PPG excursions
    - basal, prandial, and total insulin dose
    - event rate (per patient per year) of overall hypoglycemic events
- Use all data regardless of IP use:
    - treatment-emergent injection site reaction and hypersensitivity reaction

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

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

The subgroup analysis for insulin dose will use the MMRM model specified in Section 6.11.5 using the efficacy estimand. The model will include additional fixed terms of subgroup, subgroup by treatment interaction, subgroup by visit interaction, and 3-way interaction of treatment, subgroup and visit.

The treatment emergent injection site reaction and hypersensitivity reaction 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 6.6 with additional terms of subgroup, treatment by subgroup interaction will be used for the subgroup analysis of overall hypoglycemia event rate while on IP.

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

The above subgroup analyses may be repeated for the 2 double-blind treatment groups using the subgroup defined by TEADA status during the analysis period of Visit 2 to Visit 801.

6.12.7.2. Anti-Insulin Lispro Antibody Return to Baseline

Any patient who develops a TEADA response at any time during the treatment period (0 to 52 weeks for double-blind treatment groups and 0 to 26 weeks for open-label treatment group) that has not returned to baseline at Visit 801 should undergo follow-up for antibodies to insulin lispro for a maximum of 6 months after Visit 801 or until anti-insulin lispro antibodies return to baseline range, whichever occurs sooner. The analyses for return to baseline will only include patients meeting this antibody follow-up entry criteria. Return to baseline (RBL) is defined as

- not detected postbaseline anti-insulin lispro antibody level at or after Visit 801 for patients with not detected status at baseline, or
- the detected postbaseline anti-insulin lispro antibody level (percent binding) at or after Visit 801 is less than 157% of the baseline value for patients with detected status at baseline.

Reasons for discontinuation from the antibody follow-up at Visits 802 and 803 will be summarized by the randomized treatment groups. No treatment comparison will be conducted.

Duration of exposure to IP will be summarized by treatment groups. Only descriptive statistics: n, mean, SD, median, minimum, maximum, and sum (that is, total patient-years of exposure), will be provided.

The number and percentage of patients whose anti-insulin lispro antibody levels meet the RBL criteria will be summarized by visit (Visit 802, and 803).

For the patients participating in the insulin antibody follow up, a summary of HbA1c, the insulin dose (prandial, basal, and total daily insulin dose), vital signs, body weight, AEs and concomitant medications reported during the immunogenicity follow up period will be summarized by randomized treatment group. The summary will include descriptive statistics and no statistical test will be performed for treatment comparison.

A scatter plot using the antibody percent binding at the last visit in the immunogenicity follow up period as X-axis and the HbA1c value at the same visit as Y-axis will be generated. A similar scatter plot with total daily dose as Y-axis will also be generated.

6.12.8. Patient Narratives

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

- deaths
- 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.

6.13. Subgroup Analyses

6.13.1. Subgroup Analyses for HbA1c

The following subgroups will be analyzed for HbA1c if there are sufficient numbers of patients per group (for example, at least 10% in each group) using data collected from all randomized patients prior to discontinuation of IP through Week 26:

- age (<40, ≥40 years)
- hemoglobin A1c stratum (≤7.5% vs. >7.5%)
- patient's personal CGM/FGM use during the study (Yes vs. No)
- sex (male vs. female)
- body mass index (<25 vs. ≥25, and <30 vs. ≥30 kg/m^2)
- duration of diabetes (using the median as the cut-off)
- race
- ethnicity
- country
- region (Europe, North America, Eastern Asia [Japan, Taiwan, Korea], and Other [India, Mexico, Argentina, Australia, New Zealand])
- baseline 1-hour PPG excursion (≤ baseline median, > baseline median)
- baseline 1-hour PPG (PPG ≤180 mg/dl, >180 mg/dl)
- baseline 2-hour PPG excursion (≤ baseline median, > baseline median)
- baseline 2-hour PPG (PPG ≤180 mg/dl, >180 mg/dl)
- type of basal insulin during the lead-in period (glargine U-100 vs. degludec U-100)
- prandial insulin dosing plan (carbohydrate counting or pattern adjustment)

Analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 26) will be evaluated to assess the treatment by subgroup interaction. When analyzing HbA1c stratum as a subgroup the baseline HbA1c will not be included as a covariate to avoid confounding. The subgroup interaction effect will be evaluated using a significance level of 0.10, unadjusted.

Additional subgroup analyses may also be performed.

6.13.2. Subgroup Analyses for Hypoglycemic Events

For the documented symptomatic hypoglycemia based on the thresholds of blood glucose ≤70 mg/dL, the following subgroups will be analyzed using data collected from all randomized patients prior to discontinuation of IP through Week 26:

- age (<40, ≥40 years)
- hemoglobin A1c stratum (≤7.5% vs. >7.5%)
- region
- type of basal insulin during the lead-in period (glargine U-100 vs. degludec U-100)
- prandial insulin dosing plan (carbohydrate counting or pattern adjustment)
- patient's personal CGM/FGM use during the study (Yes vs. No)

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

6.14. 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.

The primary database lock will occur after all patients in the double-blind arms have either completed the Week 26 visit or discontinued from the study prior to Week 26, and after all patients in the open-label treatment group have completed Visit 801 (not including patients in Japan who will remain in the study through Week 52 before going to Visit 801). Investigators and patients will remain blinded to treatment assignments until the final database lock after all patients complete the study.

6.15. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Non-Serious Adverse Events are summarized by treatment group and 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 Serious AE, 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.

7. Unblinding Plan

The blinding and unblinding plan will be provided in a separate document stored in the Trial Master File.

8. References

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9. Appendices

Appendix 1. Empirical Estimation of Relative Event Rate

Traditionally, Poisson distribution has been assumed to draw inference for the rate of rare events. When the event is rare and the sample size is large, it is known that the overall number of events is approximately from Poisson distribution. However, for some not very rare events such as severe hypoglycemic events in T1D patients, the total number of events may not be distributed from Poisson and may be over-dispersed. Assuming Poisson distribution may significantly underestimate the variance, and therefore may reduce the overage probability and inflate the Type-I error. An empirical method in estimating the variance of the relative event rate without assuming any distribution on the number of events will be provided in this appendix.

Let X_{ij} denote the count response variable for patient j in treatment group i. Let $Y_i = \sum_j X_{ij}$ be the total number of events for treatment group i, and T_i denote the exposure for treatment group i. Let $i = 0$ for the control group and $i = 1$ for the experimental treatment group. The event rate for treatment group i can be calculated as

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 2. Statistical Analysis for Japan

Separate analyses will be performed for patients participating in Study ITRM from Japan based on the following 2 databases:

1) 26-week database: the primary database lock same as global, which will occur after all patients in the double-blind arms have either completed the Week 26 visit or discontinued from the study prior to Week 26, and after all patients (except for patients in Japan) in the open-label treatment group have completed Visit 801.
2) Japan 52-week database: the database lock which will occur after all Japanese patients who are randomized into both global and MEE cohorts have completed Visit 801. Note that the LY900014+20 treatment group will be included in the analyses for the 52-Week Treatment Period.

The analysis methods will be similar to those described for the main study. Statistical comparisons between treatment groups will be performed. Analysis models similar to the main study will be used without the model term for pooled country.

The analyses to be included will be documented in a separate list of analyses.

Appendix 3. Statistical Analysis for Maximum Extended Enrollment (MEE) Addendum

Once the protocol-defined milestone of last-patient-entered-treatment for the global study cohort is reached, the enrollment of patients will continue in Japan, Mexico, Taiwan, Russia, and India under the MEE addendum until a sufficient number of patients are enrolled to meet their country-specific regulatory requirements for submission. At least 1 patient from the indicated countries must be enrolled in the global cohort to be eligible for enrollment of subsequent patients into the MEE cohort. However, each indicated country should attempt to enroll approximately 10% of their target patient allocation in the global cohort before enrollment in the MEE cohort is started. The MEE addendum will not be implemented in these countries if the respective countries enroll sufficient number of patients in the global cohort to meet their local registration requirements.

The data from the MEE cohort will be used in the countries participating in the MEE addendum to evaluate similarity between local patients and the population enrolled in the global cohort. Country-specific efficacy and safety analyses will be summarized separately for Japan, Mexico, Taiwan, Russia, and India. These country-specific analyses will include patients from both the MEE and the global cohorts from that country. All analyses of any MEE country-specific cohort would be for submission only to that country and will not be incorporated into the analysis of the global cohort.

All analyses are for descriptive purposes and are not for comparative purposes.

A subset of the planned efficacy, health outcomes and safety analyses, which are described in ITRM SAP sections above, will be produced for each country participating in the MEE addendum, with the exception of Japan (see Appendix 2 for a description of analyses for Japan). The analyses will be similar to those planned for the global cohort; however, no statistical comparisons between treatment groups will be performed. Analysis models similar to the global cohort will be used without the model term for pooled country. Least-Squares means and 95% confidence intervals will be displayed by treatment for the analysis of continuous variables. Analyses of the 26-Week Treatment Period will include patients randomly assigned to all 3 treatment groups, and analyses of the 52-Week Treatment Period will include patients randomly assigned to the 2 double-blind treatment groups.

The analyses to be included will be documented in a separate list of analyses.

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