Statistical Analysis Plan A Prospective, Randomized, Double-Blind, Crossover Comparison Evaluating Compatibility and Safety of LY900014 and Insulin Lispro with an External Continuous Subcutaneous Insulin Infusion System in Adult Patients with Type 1 Diabetes (PRONTO-Pump)

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1. Statistical Analysis Plan: A Prospective, Randomized, Double-Blind, Crossover Comparison Evaluating Compatibility and Safety of LY900014 and Insulin Lispro with an External Continuous Subcutaneous Insulin Infusion System in Adult Patients with Type 1 Diabetes (PRONTO-Pump)

LY900014

Study I8B-MC-ITSI is a Phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter, 2-treatment group, crossover, active-controlled study conducted in patients with type 1 diabetes currently using continuous subcutaneous insulin infusion.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I8B-MC-ITSI
Phase 3

Statistical Analysis Plan electronically signed and approved by Lilly: 20 February 2018
Statistical Analysis Plan version 2 electronically signed and approved by Lilly: 26 April 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. Version 1 is based on the Protocol I8B-MC-ITSI approved on 23 October 2017 and amended on Jan 12, 2018.

SAP Version 2 was approved on 26 April 2018. The main changes from Version 1 are listed below:

- adding analysis details (for example, analysis of time until infusion set changes) and rules (for example, to define unique hypoglycemia events).
- deleting the following analyses:
    - 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

This SAP is the third version approved prior to the first unblinding. The main changes from Version 2 are listed below:

- modifying the baseline definition for treatment-emergent adverse event (TEAE) analyses for the two 6-week randomized treatment periods: use observations prior to first dose of randomized investigational product (IP) (or Visit 3 date if the dose date is missing) but after the first dose of open-label lispro in the lead-in period.
- adding treatment-emergent potential hepatic disorder analyses.
- adjusting the hypoglycemia rate analysis methods to Wilcoxon signed-rank test only and removing the basal rate from hypoglycemia incidence analysis model, to address the model convergence issue due to the relatively small sample size of the study.
- adding more details as to how to identify a non-meal related correction bolus in electronic clinical outcomes assessment (eCOA) captured data.

4. Study Objectives

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

Table ITSI.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
1. To compare LY900014 and insulin lispro with respect to the rate of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump	1. Rate (events/patient/30 days) of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump, during the 6-week treatment period
Secondary Objectives	
2. To compare LY900014 and insulin lispro with respect to the incidence of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump	2. Incidence (percent of patients with at least 1 event) of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump, during the 6-week treatment period
3. To compare LY900014 and insulin lispro with respect to the rate and incidence of premature infusion set changes	3. Rate (events/patient/30 days) and incidence of premature infusion set changes by reason (infusion set kinked, came out, or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other) during the 6-week treatment period
4. To compare LY900014 and insulin lispro with respect to the time interval until infusion set change	4. Time interval until infusion set change during the 6-week treatment period
5. To compare LY900014 and insulin lispro with respect to total, basal, and bolus insulin dose	5. Bolus/total insulin dose ratio at the end of the 6-week treatment period
6. To compare LY900014 and insulin lispro with respect to the interstitial glucose reduction rate from hyperglycemia following a non-meal-related correction bolus delivered via the pump	6. Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >180 mg/dL (10.0 mmol/L) to recovery (interstitial glucose ≤180 mg/dL), from up to 6 weeks of CGM use

Objectives	Endpoints
7. To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	7. Rate (events/patient/100 years) of severe hypoglycemic events during the 6-week treatment period
Tertiary/Exploratory Objectives	
8. To compare the safety of LY900014 and insulin lispro	8. Adverse events and vital signs
9. To compare LY900014 and insulin lispro with respect to the rate and incidence of documented symptomatic post-meal 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 post-meal hypoglycemia within 1 and 2 hours after the start of a meal during the last 2 weeks of the 6-week treatment period
10. To compare LY900014 and insulin lispro with respect to the rate and incidence 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 during the last 2 weeks of the 6-week treatment period
11. To compare LY900014 and insulin lispro with respect to the incremental AUCs after breakfast, obtained from CGM use	11. Incremental $AUC_{0\text{-}1\ hour}$ after breakfast during the last 2 weeks of up to 6 weeks of CGM use
12. To compare LY900014 and insulin lispro with respect to the duration of time glucose values are within target range (71 and 180 mg/dL [3.9 and 10.0 mmol/L]), obtained from CGM use	12. Duration (in minutes) and percentage of time with glucose values between 71 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period, during the last 2 weeks of up to 6 weeks of CGM use
13. To compare LY900014 and insulin lispro with respect to the duration of time glucose values are within target range (71 and 140 mg/dL [3.9 and 7.8 mmol/L]), obtained from CGM use	13. Duration (in minutes) and percentage of time with glucose values between 71 and 140 mg/dL (3.9 and 7.8 mmol/L), both inclusive, normalized to a 24-hour period, during the last 2 weeks of up to 6 weeks of CGM use
14. To compare LY900014 and insulin lispro with respect to the glucose profiles, obtained from CGM use	14. Average glucose for a 24-hour period during the last 2 weeks of up to 6 weeks of CGM use
15. To compare LY900014 and insulin lispro with respect to the glucose variability, obtained from CGM use	15. Interquartile range, CV, LBGI, and HBGI during the last 2 weeks of up to 6 weeks of CGM use
16. To compare LY900014 and insulin lispro with respect to the factors affecting dosing in pumps	16. Actual and change from baseline in factors affecting dosing in pump (breakfast CR, AIT, breakfast ISF, and frequency of use of non-normal bolus type [Square Wave or Dual Wave]), during the 6-week treatment period

Objectives	Endpoints
17. To compare LY900014 and insulin lispro with respect to the duration of time spent in hypoglycemic glucose ranges, obtained from CGM use	17. Duration (in minutes) and percentage of time with glucose values <50, <60, and ≤70 mg/dL (0.8, 3.3, and 3.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes <50, <60, and ≤70 mg/dL, during the last 2 weeks of up to 6 weeks of CGM use
18. To compare LY900014 and insulin lispro with respect to the duration of time spent in hyperglycemic glucose ranges, obtained from CGM use	18. Duration (in minutes) and percentage of time with glucose values >180, >250, and >300 mg/dL (10.0, 13.9, and 16.7 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes >180, >250, and >300 mg/dL, during the last 2 weeks of up to 6 weeks of CGM use
19. To separately evaluate the glycemic control of LY900014 and insulin lispro	19. Summary statistics of actual and change from baseline to Week 6 in HbA1c for each treatment
20. To compare LY900014 and insulin lispro with respect to 1,5-AG	20. Actual and change from baseline to Week 6 in 1,5-AG

Abbreviations: 1,5-AG = 1,5-anhydroglucitol; AUC = area under the curve; CGM = continuous glucose monitoring; CV = coefficient of variation; HbA1c = hemoglobin A1c; HBGI = high blood glucose index; LBGI = low blood glucose index; SMBG = self-monitored blood glucose.

5. Study Design

5.1. Summary of Study Design

Study I8B-MC-ITSI is a Phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter, 2-treatment group, crossover, active-controlled study conducted in patients with type 1 diabetes (T1DM) currently using CSII. In the 2 treatment groups, LY900014 and insulin lispro, meal bolus doses will be delivered immediately prior to each meal (0 to 2 minutes) in a double-blind manner.

The study includes a 1-week screening period and a 2-week lead-in period followed by a 2-period (Period I and Period II) crossover and a 4-week post-treatment safety follow-up. Each period of the crossover will consist of 6 weeks of treatment with no washout between periods.

Figure ITSI.5.1 illustrates the study design.

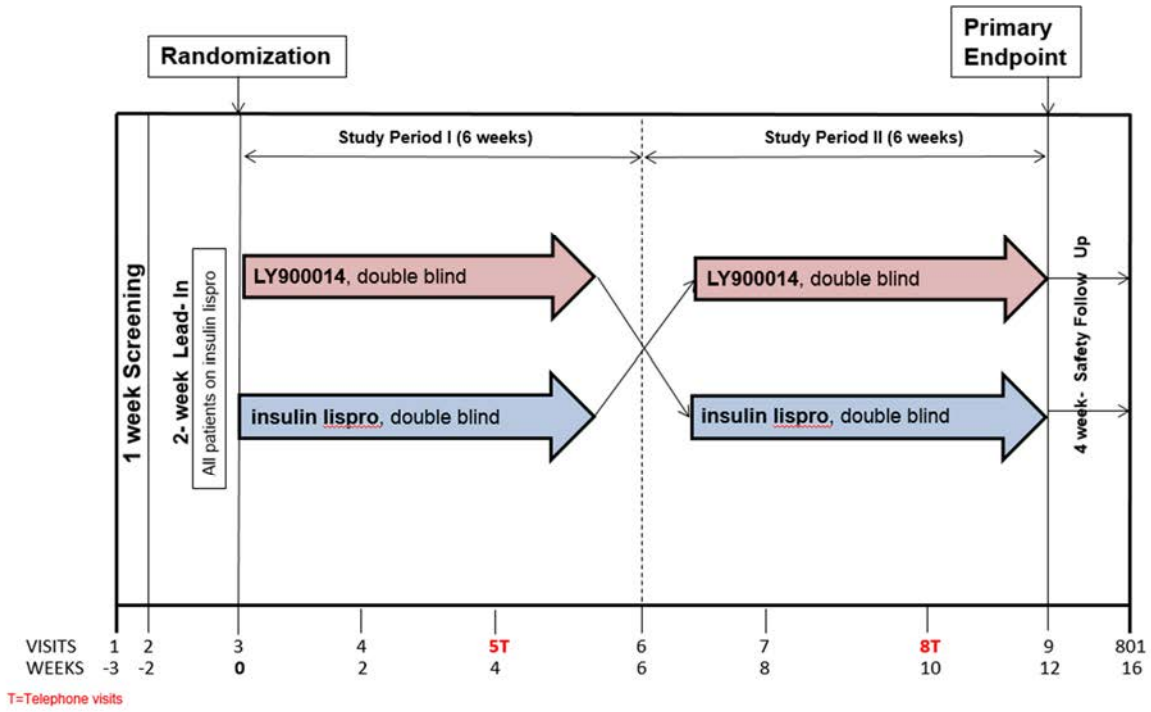

Figure ITSI.5.1. Illustration of study design for Clinical Protocol I8B-MC-ITSI.

Patients who need to discontinue from study treatment will also be discontinued from the study. Please refer to Protocol Sections 8.1 and 8.2. In this document, discontinuation of IP refers to the last dose of IP in a study period (lead-in, Period I, or Period II).

The eCOA diary will be used by patients to document 4-point SMBGs (consists of fasting [pre-morning meal], pre-midday meal, pre-evening meal, and pre-bedtime), hypoglycemia, and all infusion set changes, including date and time of change, designation of routine or premature change, primary reason for premature change (infusion set kinked, came out, or leaking; empty

pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other) as depicted in Protocol 9.1.4.1. Additional data on infusion site complications will be collected by investigators.

Patients will enter all non-meal-related correction boluses into the eCOA diary. In the case of suspected infusion set occlusion, patients will choose or enter a new correction bolus from the eCOA diary that corresponds to the time of the suspected occlusion. They will then indicate if the correction bolus was given via pump or via syringe. If more than one correction bolus is given, patients should choose the first non-meal related correction bolus. This information is also critical in order to evaluate the primary objective of the study.

Pump interruption is defined as patient is off pump due to pump malfunction and is temporarily using injection therapy. It does not include the condition where patient uses a syringe to inject a correction bolus dose while still on pump. Any interruption of CSII will need to be documented in the electronic case report form (eCRF). When patients resume use of pump following the interruption, the infusion set insertion should be entered as "routine" infusion set change in eCOA.

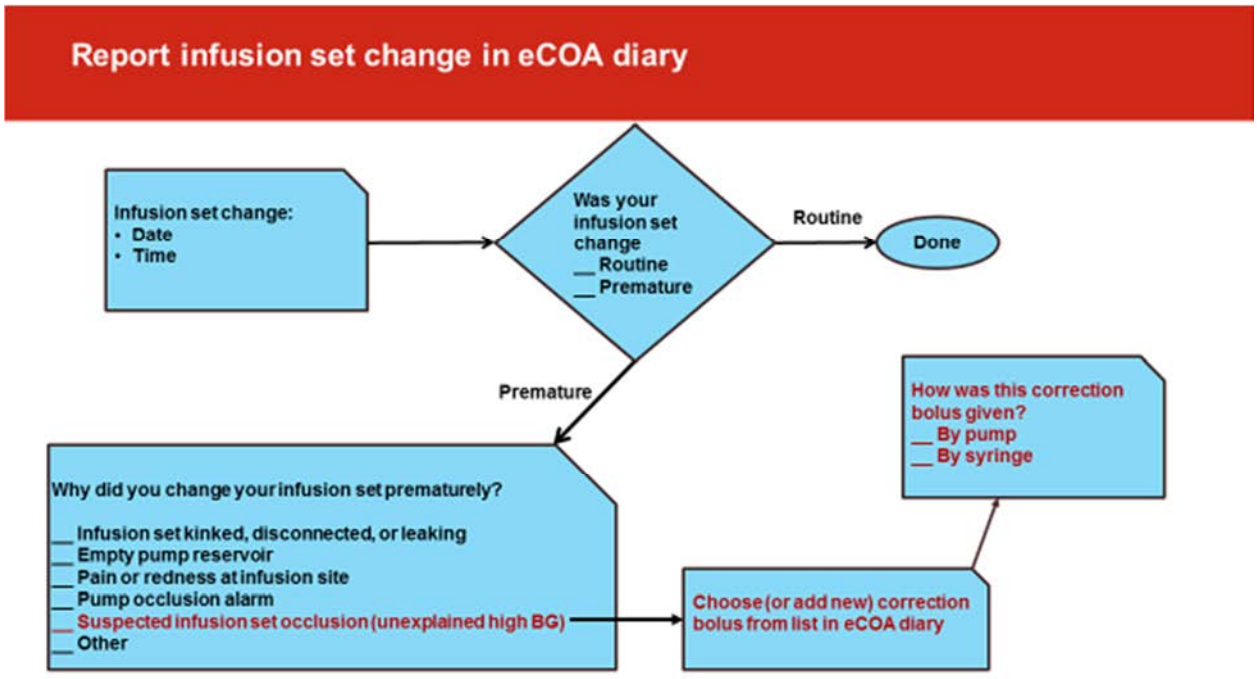

Figure ITSI.5.2. Flow chart for reporting infusion set changes.

5.2. Determination of Sample Size

Approximately 48 patients (24 patients in each treatment sequence) will be randomized in order that approximately 42 patients complete the study.

The primary objective of this study is to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood

glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump, during the 6-week treatment period.

The study was designed following a regulatory interaction to assess the safety comparability of LY900014 and insulin lispro. It is not designed or powered to be a non-inferiority or superiority trial.

Assuming a 12% dropout rate after randomization, approximately 48 patients (24 patients in each treatment sequence) will need to be randomized.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment and complete the lead-in period will be randomized to double-blind treatment at Visit 3. Assignment to treatment sequences will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

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

Sequence A: LY900014 $\rightarrow$ insulin lispro
Sequence B: insulin lispro $\rightarrow$ LY900014

Stratification will be by region (US, OUS), historical use of SmartGuard/Threshold Suspend (Yes, No), and HbA1c stratum ($\leq$7.3%, >7.3% at Visit 1).

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.

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

Table ITSI.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 2-week lead-in period.
Randomized	All patients who are randomly assigned to study treatment at Visit 3. Treatment group will be defined on the basis of the treatment the patients are assigned to.
Safety	All randomized patients who receive at least 1 dose of the randomly assigned IP. Treatment group will be defined on the basis of the treatment the patients are assigned to.
CGM Population	All randomized patients who receive at least 1 dose of the randomly assigned IP, and have CGM data from at least 1 collection period (lead-in, Period I and Period II). Treatment group will be defined on the basis of the treatment the patients are assigned to.

Safety analyses will be conducted on the Safety Population. Analyses of adverse events (AEs) will include all data collected during the course of the entire 6-week treatment period for each treatment group regardless of IP use. Analyses of hypoglycemia will be conducted on data collected prior to permanent discontinuation (i.e., last dose) of IP in each 6-week treatment period. Unless otherwise specified, pump-related safety analyses (e.g., infusion set failures, interstitial glucose reduction rate) will exclude data (if any) that are collected while patients temporarily are off pump or off IP. Data collected during the safety follow-up period will not be used for comparisons between treatment groups.

Unless otherwise specified, exploratory efficacy analyses will be conducted on the Randomized Population. CGM outcome analyses will be conducted on the CGM Population.

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

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

- Lead-in Period – Visits 2-3
- 12-Week Treatment Period while on IP – from first dose to last dose of IP in each 6-week randomized treatment period (Period I and Period II)
- 12-Week Treatment Period Regardless of IP use – from randomization to Week 6 of each randomized treatment period (including all data regardless of IP use)
- Safety Follow-up Period – Visit 801

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

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

- for data only measured at an office visit (for example, HbA1c), if the office visit date (or laboratory sample collection date) is within 14 days of the date of last study drug dose of the randomized treatment period (Period I or Period II), then postbaseline data measured at or prior to that office visit will be considered as data on IP.
- for data collected as running records with an exact date and/or time stamp such as diary entries where the date and time of the measures was not tied with the date of an office visit, postbaseline data with date and time ≤ (last study drug dose date and time) will be considered as data on IP.

For continuous measures, summary statistics will include sample size, mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. Least squares (LS) means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons.

Unless otherwise specified, a restricted maximum likelihood based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit during the 6-week treatment period for each treatment group will be included in the analysis. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on LS means and Type III tests. SAS PROC MIXED will be used to perform the analysis.

- MMRM-Model 1: for analysis of variables that are measured at multiple designated visits within each randomized treatment period (e.g., weight and vital signs), the model will include the fixed class effects of treatment, period, sequence, strata (region, historical use of SmartGuard/Threshold Suspend, HbA1c), week (relative to the start of each randomized treatment period), and week-by-treatment interaction, and the continuous, fixed covariate of baseline value. If the analysis fails to converge, the following covariance structures will be tested in order:

  - Compound symmetry with heterogeneous variances
  - Compound symmetry without heterogeneous variances
- MMRM-Model 2: for analysis of variables that are only measured once for each randomized treatment period (e.g., 1,5 AG), the model will include the fixed class effects of treatment, period, sequence, strata (region, historical use of SmartGuard/Threshold Suspend, HbA1c), and the continuous, fixed covariate of baseline value (Grizzle 1965). If this analysis fails to converge, a covariance structure of compound symmetry without heterogeneous variances will be used.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. For either of the two models, if the model fails to converge for any covariance structure, strata may be deleted from the model.

For categorical measures (such as incidence of AEs), summary statistics will include sample size, frequency, and percentages. Prescott's test will be used for treatment comparisons, unless otherwise specified.

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

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

Study Period/Analysis	Patient Population	Baseline Observations	Post-Baseline Observations
Lead-In Period (Overall[1] only)			
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 first dose of IP (or Visit 3 date if the dose date is missing)
Basal, bolus, and total insulin doses, and bolus/total insulin dose ratios continuous analysis	All Randomized Patients	Visit 2	Visit 3 prior to first dose of IP
Weight and vital signs	All Randomized Patients	Last of Visits 1-2	Visit 3
Pump factors - breakfast CR, AIT, breakfast ISF)	All Randomized Patients	Visits 2	Visit 3 prior to first dose of IP, excluding data (if any) that are collected while patients temporarily are off pump or off open-label insulin lispro
Pump factor - frequency of use of non-normal bolus type [Square Wave or Dual Wave] [3]	Population with a baseline and at least one post-baseline observation	Visit 2	Visit 3

Study Period/Analysis	Patient Population	Baseline Observations	Post-Baseline Observations
12-Week Treatment Period While on IP (from first to last dose of IP in each 6-week randomized treatment period)			
Infusion set failures	All Patients in the Safety Population	From first to last dose of open-label insulin lispro, excluding data (if any) that are collected while patients temporarily are off pump or off open-label insulin lispro	From first to last dose of IP in each randomized treatment period (Period I and Period II), excluding data (if any) that are collected while patients temporarily are off pump or off IP
Premature infusion set changes by reason (infusion set kinked, came out or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other)	All Patients in the Safety Population	From first to last dose of open-label insulin lispro, excluding data (if any) that are collected while patients temporarily are off pump or off open-label insulin lispro	From first to last dose of IP in each randomized treatment period (Period I and Period II), excluding data (if any) that are collected while patients temporarily are off pump or off IP
Time interval until infusion set change	All Patients in the Safety Population with a baseline and a post-baseline observation	From first to last dose of open-label insulin lispro, excluding data (if any) that are collected while patients temporarily are off pump or off open-label insulin lispro	From first to last dose of IP in each randomized treatment period (Period I and Period II), excluding data (if any) that are collected while patients temporarily are off pump or off IP
Basal, bolus, and total insulin doses, bolus/total insulin dose ratios	All Patients in the Randomized Population with a baseline and a post-baseline observation	Visit 3 prior to first dose of IP	Visits 4, 6, 7, and 9 prior to last dose of IP in each randomized treatment period (Period I and Period II)
CGM outcome variables (including interstitial glucose reduction rate)	All Patients in the CGM Population (with a baseline and a post-baseline observation for continuous variables, unless otherwise[2])	From first to last dose of open-label insulin lispro, excluding data (if any) that are collected while patients temporarily are off pump or off open-label insulin lispro	From first to last dose of IP in each randomized treatment period (Period I and Period II), excluding data (if any) that are collected while patients temporarily are off pump or off IP
Hypoglycemia events	All Patients in the Safety Population	From first to last dose of open-label insulin lispro	Visits 4, 5, 6, 7, 8 and 9 after first dose of IP and prior to last dose of IP in each randomized treatment period (Period I and Period II)
HbA1c summary statistics	All Randomized Patients with a baseline and at least one post-baseline observation while on IP	Last of Visit 1-3 prior to the first dose of IP	Visits 6 and 9

Study Period/Analysis	Patient Population	Baseline Observations	Post-Baseline Observations
1,5 AG	All Randomized Patients with a baseline and at least one post-baseline observation while on IP	Last of Visit 1-3 prior to the first dose of IP	Visits 6 and 9
Pump factors - breakfast CR, AIT, breakfast ISF)	All Patients in the Safety Population with a baseline and at least one post-baseline observation	Visit 3 prior to the first dose of IP excluding data (if any) that are collected while patients temporarily are off pump or off open-label insulin lispro	Visits 4, 6, 7, and 9 prior to last dose in IP of each randomized treatment period (Period I and Period II) excluding data (if any) that are collected while patients temporarily are off pump or off IP
Pump factor - frequency of use of non-normal bolus type [Square Wave or Dual Wave][3]	Population with a baseline and at least one post-baseline observation	Visit 3	Visit 4, 6, 7, 9
12-Week Treatment Period Regardless of IP use (from randomization to Week 6 of each randomized treatment period regardless of IP use)			
TEAEs	All Patients in the Safety Population	Prior to first dose of randomized IP (or Visit 3 if the dose date is missing) but after the first dose of open-label insulin lispro in the lead-in period	From randomization to Week 6 of each randomized treatment period regardless of IP use
Weight and vital signs	All Patients in the Safety Population with a baseline and a post-baseline observation	Last of Visits 2-3	Visits 4, 6, 7, and 9 regardless of IP use
Safety Follow-Up Visit (Overall[1] Only)			
TEAEs	All Patients in the Safety Population who enter the safety follow-up period	After first dose of IP and prior to last dose of IP in the 12-Week Treatment Period	From the date of the last visit of the 12-Week treatment period to the end of study
Weight and vital signs	All Patients in the Safety Population who enter the safety follow-up period	Last of Visits 2-3	Visits 801

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; CGM = Continuously Glucose Monitoring; CR = carb ratio; HbA1c = hemoglobin A1c; IP = investigational product; MMRM = mixed-effect model repeated measures; SMBG = self-monitored blood glucose; TEAE = treatment-emergent adverse event

Note:

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

[2] Not required for the interstitial glucose reduction rate and duration of each individual hypoglycemic episode because it is possible that some patients may not have any non-meal related correction bolus or hypoglycemic event to baseline values.

[3] Per protocol, pump factor - frequency of use of non-normal bolus type [Square Wave or Dual Wave] were collected over the 7 days prior to designated visits, when patients were on pump and on IP.

6.2. Adjustments for Covariates

Stratification factors of this study include region (US, OUS), historical use of SmartGuard/Threshold Suspend (Yes, No) and HbA1c stratum (≤7.3%, >7.3%). Stratification factors will be entered into the IWRS for randomization and also collected in the database by eCRF or central laboratory. The analysis models will use the stratification factors as collected in the database.

Other analyses will include the stratification factors as noted in Sections 6.11 to 6.14.

6.3. Handling of Dropouts or Missing Data

For continuous variables, missing data will be addressed by using a MMRM analysis for continuous longitudinal variables. The MMRM model provides consistent estimator when data is missing at random. The model implicitly adjusts for missing data through a variance-covariance structure.

Otherwise, handling of dropouts or missing data is described for each individual primary or secondary endpoint in Sections 6.11 to 6.13.

6.4. Multicenter Studies

This study is conducted at multiple investigators sites in U.S and Spain. All analyses using region in the model will use region (US, OUS), unless otherwise specified.

6.5. Multiple Comparisons/Multiplicity

Treatment group comparisons will be performed for the primary objective (Section 6.11.1) at the full significance level of 0.05. No multiplicity adjustments will be made for secondary and exploratory objectives.

6.6. Patient Disposition

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

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

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

A listing of the primary reason for 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 treatment sequences and the number of patients who discontinue the study.

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

6.7. Patient Characteristics

A summary table for overall and by treatment sequence 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 <65, ≥65 to <75, ≥75 to <85, ≥85 years), sex, country, region, ethnicity, race, height, weight, body mass index (BMI), BMI groups (<25, ≥25 to <30, ≥30 to <35, and ≥35 kg/m2). No statistical comparisons between treatment sequences will be performed. For continuous variables, the following statistics will be provided: mean, SD, minimum, maximum, and median. For categorical variables, summary statistics will include sample size, frequency and percentage. A listing of patient characteristics at baseline will be provided.

A similar summary of diabetes characteristics will also be generated. The following variables will be included but not limited to: duration of diabetes, duration of CSII use, pump model, the type of rapid-insulin at study entry, total daily dose at study entry, historical use of SmartGuard/Threshold Suspend at study entry, HbA1c at study entry and baseline, HbA1c stratum at baseline.

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

The total daily insulin dose for the last 3 days prior to screening will be entered into the eCRF. The dose at study entry will be calculated as the mean of the doses for the last 3 days prior to the visit. Doses will be summarized in U and U/kg. Total daily insulin dose will also be presented by the definitions in protocol exclusion criterion #28 (≤1.2 U/kg, >1.2 U/kg).

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

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

6.8. Treatment Compliance

No analysis for treatment compliance is planned for this study.

6.9. Important Protocol Deviations

Important protocol deviations that potentially compromise data integrity or patients' safety will be summarized by treatment group for all randomized patients. Table ITSI.6.3 lists the categories/subcategories of important protocol deviations, source of identification, and the method to identify each deviation.

Table ITSI.6.3. Description of Important Protocol Deviations

Category	Sub-categories	Trial Specific	Source	Methods of Identification
Informed Consent	Informed Consent Not Obtained	N/A	Mixed (monitoring and clinical database)	Compare all assessment dates to ICD date (except those assessments that may occur before ICD, e.g., disease assessments).
Informed Consent	Improper Consent	N/A	Mixed (monitoring and clinical database)	Failure to reconsent after an ICD amendment at first possible visit. Unauthorized personnel administered ICD. Patient signed incorrect version of ICD. ICD was not dated. ICD was lost.
Informed Consent	Revoke Consent	N/A	Mixed (Monitoring and clinical database)	Patient revoked ICD. If patient revokes consent, data are excluded from the study.
Eligibility	Inclusion/Exclusion	Type of Patient and Disease Characteristics	Mixed (monitoring and clinical database)	CRF (Medical History: Diabetes Duration panel) data indicate diagnosis date of T1D <1 year prior to screening date (#1). CRF (Prior Diabetes Therapies/Concomitant panel) data to indicate start date for continuously using insulin < 1 year prior to screening date (#1). Also identified by CRA as captured in sCTMS.

Category	Sub-categories	Trial Specific	Source	Methods of Identification
Eligibility	Inclusion/Exclusion	Age not in compliance with entry criteria	Mixed (monitoring and clinical database)	CRF data indicate the age <18 yrs at Visit 1 (#2). Also identified by CRA as captured in sCTMS.
Eligibility	Inclusion/Exclusion	Previous non-insulin antihyperglycemic medications	Mixed (monitoring and clinical database)	CRF Prior Diabetes Therapies / Concomitant Therapy panel data to indicate not compliant with entry criteria #42. 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 #5 [basal insulin was used for >14 consecutive days during the 6 months prior to screening], #6, or #41 Also identified by CRA as captured in sCTMS.
Eligibility	Inclusion/Exclusion	Other Inadvertent Enrollment	Non Programmable (monitoring)	Identified by CRA as captured in sCTMS.
Eligibility	Inclusion/Exclusion	Use of non-study device or materials	Non Programmable (monitoring)	Use of non-study pumps, infusion sets, and use of Enlite sensor (enables Smart-Guard)
Investigational Product	Treatment Assignment/ Randomization Error	N/A	Non Programmable (monitoring)	IWRS data entry errors that impact patient stratification, for example, lab data indicated different strata from IWRS stratification report. Dispensing error: Patient is assigned to a treatment, but site gave a different treatment to the patient.
Investigational Product	Unblinding	N/A	Non Programmable (monitoring)	Any inadvertent unblinding affecting, patients, investigator or sponsor.
Investigational Product	Patient Took Medication Not Fit for Use	N/A	Non Programmable (monitoring)	Study Drug not fit for use administered to patient.

Category	Sub-categories	Trial Specific	Source	Methods of Identification
Investigational Product	Other	Use of expired CT material	Non Programmable (monitoring)	Also identified by CRA as captured in sCTMS.
Study Procedures	Other	Infusion set change frequency	Programmable (clinical database)	eCOA data indicate that ≥75% of routine infusion set changes are not in the range of 72 ± 4 hours during the two 6-week treatment periods (#13).
Study Procedures	Violation of Discontinuation Criteria	N/A	Mixed (monitoring and clinical database)	Patients not discontinued from study despite having met protocol specified discontinuation criteria. Also identified by CRA as captured in sCTMS. Protocol Section 8 (e.g., patient(s) become pregnant according to central/local lab or CRF AE page).
Study Procedures	Excluded Conmeds	N/A	Mixed (monitoring and clinical database)	CRF Prior Diabetes Therapies / Concomitant Therapy panel data to indicate not compliant with entry criteria #43 and study-specific restriction on concomitant therapies Table ITSI.5 in the study protocol. Also identified by CRA as captured in sCTMS.
Study Procedures	Visit Schedule Criteria	N/A	Programmable (clinical database)	CRF data indicate that two consecutive office visits are completely missing.
Study Procedures	Other	Electronic Clinical Outcomes Assessment (eCOA)	Mixed (monitoring and clinical database)	Patients did not use eCOA system during the entire study. Comparison of patient data from CRF and eCOA to identify randomized patients who have no eCOA data entered.
Administrative/ Oversight	Suspected Misconduct	N/A	Non Programmable (monitoring)	Site staff sharing account details for systems (e.g., IWRS, EDC, eConsent or ePresentOnline). Suspected falsification of data.

Category	Sub-categories	Trial Specific	Source	Methods of Identification
Administrative/ Oversight	PI oversight	N/A	Non Programmable (monitoring)	Identified by CRA as captured in sCTMS.
Safety	Safety Mailings	N/A	Non Programmable (monitoring)	Lack of, significant delay in safety mailing review (significant delay defined as a delay of 1 month).
Safety	SAEs	Failure to report SAE in 24 hours	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.
Safety	Other	Failure to report product complaint within 24 hours	Non Programmable (monitoring)	Identified by CRA as captured in sCTMS.

Abbreviations: CRA = clinical research associate; CRF = clinical (case) report form; CT = clinical trial; ICD = informed consent document; EDC = Electronic Data Capture; ITSI = Study I8B-MC-ITSI; IWRS = interactive Web Response System; OAM = oral antihyperglycemic medication; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; SAE = serious adverse event; sCTMS = Simplicity Clinical Trial Management System; T1D = type 1 diabetes; yrs = years.

#: number of inclusion/exclusion criteria in the protocol.

The listing of important protocol deviations for all randomized patients during the entire study, will be provided in the CSR.

6.10. Concomitant and Prior Therapy

Concomitant medications will be summarized and compared between treatment groups using Prescott's exact test for the Randomized Population during the 2 randomized treatment periods (Period I and Period II). The percentages of patients receiving each concomitant medication will be summarized by treatment using preferred term nested within Anatomical Therapeutic Chemical (ATC) Level 3 code. Medications will be ordered by decreasing frequency within ATC level. Concomitant medication used during the lead-in period will also be summarized for the Enrolled Population.

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

The daily basal dose, daily bolus dose, total insulin dose, and the ratio of bolus dose to total insulin dose during the lead-in period will be summarized by visit for overall and by treatment sequence. The doses and bolus/total insulin dose ratios for each visit will be calculated as the mean of the doses for the last 3 days prior to the visit date that are entered in the eCRF. Doses will be summarized in U and U/kg.

6.11. Safety Analyses

6.11.1. Primary Outcome and Methodology

The primary objective of this study is to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump, during the 6-week treatment period.

To be considered as the primary endpoint, an infusion set failure must result in a premature infusion set change due to:

1. pump occlusion alarm(s), OR
2. unexplained hyperglycemia that meets the following conditions:
   - Associated with a non-meal-related correction bolus delivered via the pump at least 1 hour before the infusion set change
   - Most recent self-monitored blood glucose (SMBG) within 1 hour before the correction bolus >250 mg/dL (13.9 mmol/L)
   - At least 1 SMBG obtained following the correction bolus prior to the infusion set change
   - Within 1 hour (+10 minutes) following the correction bolus, the most recent SMBG prior to the infusion set change does not indicate a decrease in blood glucose

If more than 1 non-meal-related correction bolus is given for an unexplained hyperglycemia, only the first correction bolus time will be used to determine the 1 hour (+10 minutes) timeframe following the correction bolus as described in Section 9.1.4.1.2 of the protocol.

For each treatment period (lead-in, Period I and Period II), the infusion set failure rate (events/patient/30 days) will be calculated for each patient as the total number of events while the patient is on pump and on study treatment divided by the days of exposure [last dose date and time – first dose date and time – duration of pump or treatment interruption] times 30.

The analyses of the primary objective will be conducted on the Safety Population including data collected prior to permanent discontinuation of investigational product (i.e., last dose) in each randomized treatment period (Period I and Period II) and excluding data (if any) that are collected while patients temporarily are off pump or off IP. Treatment group comparisons will be performed using Wilcoxon signed-rank test at the full significance level of 0.05, with patients who are dosed in both treatment periods.

6.11.2. Other Secondary Safety Analyses

The analyses described in Section 6.11.2 will include data collected for the Safety Population including data collected prior to permanent discontinuation (i.e., last dose) of IP in each 6-week treatment period. In addition, other than severe hypoglycemia events, all secondary safety endpoints are pump-related, and therefore the corresponding analyses will also exclude data (if any) that are collected while patients temporarily are off pump or off IP.

For the following secondary safety endpoints, the incidence (percent of patients with at least 1 event) and rate will be analyzed using Prescott's exact test and Wilcoxon signed-rank test, respectively, as described above for the primary endpoint.

- suspected infusion set occlusions defined as unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour (+10 minutes) following a correction bolus delivered via the pump and that leads to an infusion set change
- infusion set failures leading to premature infusion set changes due to unexplained hyperglycemia with blood glucose >250 mg/dL that does not decrease by >50 mg/dL within 1 hour (+10 minutes) following a correction bolus delivered via the pump
- premature infusion set changes for any reason and for each individual reason (infusion set kinked, came out or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other)
- severe hypoglycemic events

For the infusion set failures and premature infusion set changes, the number of events and the number of patients with events will be derived for each treatment group by infusion set catheter dwell time (≤24 hours, >24 and ≤48 hours, >48 and ≤72 hour, >72 hours), and overall (across over the course of approximately 72-hours of continuous infusion).

A listing of premature infusion set changes due to unexplained hyperglycemia will be generated. For each premature infusion set change due to unexplained hyperglycemia, the following information will be provided:

- whether it is an infusion set failure that meets the primary endpoint definition
- whether it is an infusion set failure that meets the secondary endpoint definition (i.e. leads to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose [SMBG] >250 mg/dL [13.9 mmol/L] that does not decrease by >50 mg/dL within 1 hour [+10 minutes] following a correction bolus delivered via the pump)
- the most recent SMBG within 1 hour before the correction bolus
- the 3 most recent CGM values within 20 minutes before the correction bolus
- the most recent SMBG within 1 hour (+10 minutes) following the correction bolus that was collected prior to the infusion set change
- the most recent SMBG within 2 hours (+10 minutes) following the correction bolus that was collected prior to the infusion set change
- the 3 CGM measures within the time interval of [1 hour-10 minutes, 1 hour+10 minutes] following the correction bolus that were collected prior to the infusion set change
- the 3 CGM measures within the time interval of [2 hour-10 minutes, 2 hour+10 minutes] following the correction bolus that were collected prior to the infusion set change
- the highest ketone testing value within ±2 hours of the correction bolus
- the highest ketone test value within ±2 hours of the infusion set change

Similarly, a listing of premature infusion set changes due to pump alarms and a listing of all premature infusion set changes will also be provided. The SMBG values, CGM values, and ketone test values relative to the infusion set change time will be provided. Both date and time

of all infusion set changes will be collected in the database by either eCRF or eCOA (Table ITSI.6.4).

Table ITSI.6.4. Source Data for Infusion Set Changes

Study Period	Infusion Set Changes	Data Source
Lead-in period	First infusion set change	eCRF: First Dose Open Label Lead-in Treatment
	Other infusion set changes- outside of the office visit	eCOA
	Last infusion set change	eCRF: Last Dose Open Label Lead-in Treatment[a]
Period I	First infusion set change	eCRF: First Dose Study Treatment Period I
	Other infusion set changes – outside of the office visit	eCOA
	Last infusion set change	eCRF: Last Dose Study Treatment Period I[a]
Period II	First infusion set change	eCRF: First Dose Study Treatment Period II
	Other infusion set changes – outside of the office visit	eCOA
	Last infusion set change	eCRF: Last Dose Study Treatment Period II[a]
Safety Follow-up	NA	NA

[a] In extremely rare cases where patients stopped treatment on pump but continued to use treatment through syringe until they discontinue from the study, the last dose form will capture the timing of the last dose of treatment in CRF, which will not be the last infusion set change.

The last infusion set change in each treatment period (lead-in, Period I or Period II) occurs only when a patient comes to an office visit or early discontinuation of study treatment. This change is not reflective of patients' behavior regarding infusion set changes, and thus it will not be included in the derivation of time until infusion set changes. Patient-reported premature infusion set changes due to the reason "Other" or patient-reported routine infusion set changes that occur within 1 hour of a previous infusion set change (captured in the case report form [CRF]), will be treated as a redundant entry in eCOA and excluded from all analyses. In addition, any patient-reported routine infusion set change that occurred within 24 hours of a previous infusion set change could have been misreported as routine or are redundant entries in eCOA, and thus will be excluded from all analyses.

Time interval until infusion set change for each infusion set can be derived through a minute-to-day conversion by dividing the time difference between the infusion set change and its previous infusion set change by 1440 minutes. The protocol requires that patients change infusion set every 72 ± 4 hours unless a change is required for failure of the infusion set. To handle potential missing input in eCOA for the infusion set change, time interval until infusion set change greater than 7 days (168 hours) will be excluded. For each treatment period, time interval until infusion set change will be derived by averaging all infusion set changes within the period. The analyses will be conducted by an MMRM model (Model 2) as specified in Section 6.1.

Derivation and analysis of interstitial glucose reduction rate are described in Section 6.12.

Actual and change from baseline in total, basal, and bolus insulin doses and bolus/total insulin dose ratios will be compared between LY900014 and insulin lispro using an MMRM model (Model 1) as specified in Section 6.1. The doses and bolus/total insulin dose ratios for each visit will be calculated as the mean of the doses for the last 3 days prior to the visit. A listing of insulin doses will also be provided, including data collected at Visit 801.

6.11.3. Pump Factors

Actual and change from baseline in pump factors affecting insulin dosing, including breakfast CR, AIT, breakfast ISF, and frequency of use of non-normal bolus type (Square wave or Dual Wave), will be summarized and compared between LY900014 and insulin lispro using an MMRM models as specified in Section 6.1.

For each patient, frequency of use of non-normal bolus type at a visit will be calculated as the total number of meal-related bolus doses given as Square Wave or Dual Wave during the 7 days prior to the visit date divided by the total number of meal-related bolus doses during the 7 days prior to the visit date.

A listing of these pump factors will also be provided, including data collected at Visit 801.

6.11.4. Extent of Exposure

Duration of exposure to study drug will be summarized. The following summary statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (that is, total patient-years of exposure). The number and proportion of patients falling into the following different exposure categories will also be summarized: <7 days (>0 and <7 days), ≥7 and <14 days , ≥14 and <28 days, ≥28 days and < 42 days) and ≥42 days.

Patients who complete the study treatment period are required to complete a safety follow-up visit without study drug; and patients who discontinue the IP prematurely are required to discontinue from the study (ITSI Protocol 8.1-8.2).

6.11.5. Adverse Events

Events that are newly reported after the first dose of rapid-acting insulin provided as study drug (i.e., open-label insulin lispro used during the lead-in period or IP used during each of the two 6-week randomized treatment periods) or are reported to worsen in severity from baseline (defined

in Table ITSI.6.6 for each specific study period) will be considered TEAEs. Events that continue during more than 1 study period (lead-in, Period I, Period II) with the same severity will only be counted once for the first study period.

The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity. For events occurring on the day of first dose of blinded bolus insulin provided in this study during each treatment period (lead-in, Period I and Period II), the CRF-collected flag will be used to determine whether the event started or worsened post-treatment, and/or the treatment of which period the AE should be assigned.

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

The number and percentage of patients with SAEs and who discontinued from the study due to an AE will be summarized using MedDRA Preferred Term (PT) nested within System Organ Class (SOC). Prescott's exact test will be performed for treatment comparison.

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

The number and percentage of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT (without regard to SOC). For each patient and TEAE on each treatment, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT during the corresponding randomized treatment period for the specified treatment. No statistical comparison between treatment groups will be conducted.

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

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

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

Table ITSI.6.5 summarizes the planned analyses and the requirement of analysis data for different analysis periods.

Table ITSI.6.5. 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 due to AE	N/A	Open-label insulin lispro
Treatment Period (0-12 Weeks)	Safety Population	AE overview; TEAE by SOC and by PT; TEAEs by maximum severity; SAE; discontinuation due to AE; other notable AEs	All data regardless of IP use	LY900014, insulin lispro
Safety Follow-up Period	All Patients in the Safety Population who enter follow-up period	TEAE by PT	All data	Overall[a]

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

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

6.11.6. 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 sequence, treatment group, baseline age, sex, associated AE, first and last dose date for open label insulin lispro and randomized IP, and the event date.

6.11.7. Hypoglycemic Events and Other Adverse Events

The analysis plans for the following adverse events are discussed in Section 6.11.7.1 through Section 6.11.8:

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

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

6.11.7.1. Hypoglycemic Events

Hypoglycemia events that occur during the study 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, 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.

Table ITSI.6.6 provides detailed statistical methods for each endpoint related to hypoglycemia. For these analyses, hypoglycemia events prior to the discontinuation (i.e., last dose) of IP will be summarized. Additional analyses for other types of hypoglycemic events not mentioned in the table may be conducted as needed.

A listing of patients with at least 1 severe hypoglycemia reported (as SAE) after randomization (including Visit 801) will be provided.

A list of MedDRA PTs will be used for the narrow search of potential severe hypoglycemia in spontaneously reported AEs. The events identified through the search strategy that are also reported as SAEs will be summarized and compared between treatments. Prescott's exact test will be used to assess the treatment difference in the proportion of patients with potential severe hypoglycemia.

Table ITSI.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, 0-6, 4-6 weeks	Wilcoxon signed-rank test will be conducted.

Endpoint	Analysis Period	Statistical Method
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, 0-6, 4-6 weeks	If there are ≥5 patients with at least one event within the specified time period, a generalized linear mixed model with options of the binomial distribution and logit link function with treatment, period, sequence. The within-patient error will be modeled as a compound symmetry without heterogeneous variance-covariance matrix. If the model does not converge, Prescott's exact test will be conducted.
Rate of post-meal hypoglycemic events (per patient per 30 days / year) • 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 0-4, 0-6, and 4-6 weeks	Wilcoxon signed-rank test will be conducted.
Incidence of post-meal hypoglycemic events • 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 0-4, 0-6, and 4-6 weeks	If there are ≥5 patients with at least one event within the specified time period, a generalized linear mixed model with options of the binomial distribution and logit link function with treatment, period, sequence. The within-patient error will be modeled as a compound symmetry without heterogeneous variance-covariance matrix. If the model does not converge, Prescott's exact test will be conducted.
Rate of severe hypoglycemic events (per patient per year / 100 years)	0-4, 0-6, 4-6 weeks	Exposure adjusted rate per year / 100 years (calculated for each patient by total number of events divided by total exposure) will be provided and Wilcoxon signed-rank test will be used for treatment comparison.
Incidence of severe hypoglycemic events	0-4, 0-6, 4-6 weeks	Proportion of patients with severe hypoglycemia will be reported. The treatment comparison will be based on Prescott's exact test.

[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 post-meal hypoglycemia for which only the threshold of ≤70 mg/dL will be applied.

6.11.7.2. 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 Prescott's exact test. The following Standardised MedDRA Query (SMQ) will be used to identify potential systemic hypersensitivity reactions from all TEAEs:

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

event that is in category C) or (had at least 1 event that is in category D and [also had at least 1 event in category B or at least 1 event in category C])
- Angioedema (SMQ)
- Hypersensitivity (SMQ)

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

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

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

6.11.7.3. Infusion Site Reaction

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

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

6.11.7.4. Hepatobiliary Events

6.11.7.4.1. 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, and ordered by decreasing frequency. The following SMQs based on MedDRA will be used to identify potential hepatic disorders:

- Broad and narrow terms in the Liver related investigations, signs and symptoms SMQ (20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009)
- Broad and narrow terms in the Hepatitis non-infections SMQ (20000010)
- Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)
- Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015)

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

6.11.7.5. Malignant Neoplasm Events

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

6.11.8. Blood Ketones

Blood ketones should be tested with the meter provided when unexplained hyperglycemia occurs with blood glucose >250 mg/dL (13.9 mmol/L) or a pump occlusion alarm occurs with blood glucose >250 mg/dL (13.9 mmol/L). If a test is performed, ketone values should be documented in the eCRF and will be presented by (≤0.6 mmol/L, >0.6 mmol/L) for each treatment group. There will be no statistical comparison between treatments.

6.11.9. Clinical Laboratory Evaluation

The data from safety laboratory measures will be only collected at Visit 1 and Visit 2 for patient safety. Therefore no by-treatment group summary or statistical analysis will be provided.

6.11.10. Vital Signs and Other Physical Findings

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

The measurements during the treatment period (0-12 weeks) will be analyzed by MMRM model with treatment, baseline value of the response variable, sequence, period, week (defined from the start of each randomized treatment period), and week by treatment interaction as fixed factors and patient as the random factor.

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

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

visits to a value greater than the high limit at any time that meets the specified change criteria during the 2 randomized treatment periods. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time that meets the specified change criteria during the 2 randomized treatment periods. Table ITSI.6.7 will be used to define the low and high limits and change thresholds.

Table ITSI.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.

6.11.11. 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 insulin treatment. Therefore, the blood sample result at Visit 2 will be considered as the anti-insulin lispro level at baseline for this study.

6.11.11.1. 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 post-baseline (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 post-baseline detected anti-insulin lispro;
- treatment-boosted response: change from detected anti-insulin lispro at baseline (Visit 2) to post-baseline 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 study (from Visit 2 to Visit 801) will be summarized for the Safety Population overall. For patients with positive TEADA response any time during the study, the number and percentage of patients with positive insulin cross-reactivity anytime during the study, and the number and percentage of patients not meeting the TEADA criteria at Visit 801 will also be summarized for overall. No statistical comparisons between treatment groups will be conducted because patients were exposed to both LY900014 and Humalog due to the crossover design.

The anti-insulin lispro antibody level in percent binding will be summarized by scheduled visit prespecified in the protocol for patients with positive TEADA response from Visit 2 to Visit 801.

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

6.11.12. Patient Narratives

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

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

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

6.12. CGM Analyses

The analyses described in Section 6.12 will include data collected from first dose to last dose of study drug (i.e., open-label insulin lispro used during the lead-in period or IP used during each of the randomized treatment periods [Period I and Period II]) , excluding data (if any) that are collected while patients temporarily are off pump or off study treatment.

All of the variables will be derived for the lead-in period, Period I and Period II. For the lead-in period, the variables will be derived based upon the data collected during the 2-week open-label lispro treatment period. For Period I and Period II, the variables will be derived for 0-4, 0-6, and 4-6 weeks relative to the start of each randomized treatment period, respectively. For the interstitial glucose reduction rate, treatment comparisons will be based upon the derived outcome variables for 0-6 weeks. For other variables, treatment comparisons will be based upon the derived outcome variables for 4-6 weeks.

Table ITSI.6.8 lists all numerical measures for CGM data, including all secondary and exploratory CGM outcome variables.

To ensure that the CGM outcome variables are only calculated from CGM session days with sufficient data within the 24-hour, daytime (0600 hours to midnight), or nighttime (midnight to 0600 hours) periods, the following criteria will be used to determine a valid CGM session day to be counted into the calculation for a visit: 1) minimum number of measures per day – at least 70% of the total measures that are supposed to be obtained (for example, 70% of the 288 measures for the 24-hour period or 70% of 72 measures for the nighttime period); 2) maximum allowable missing interval – no interval greater than 3 hours between non-missing measures.

Similarly, for the by-meal outcome variables, the following criteria will be used to determine a valid CGM session day for a visit: 1) minimum number of measures per day – at least 70% of the total measures that are supposed to be obtained. For example, 70% of the 24 measures for the $iAUC_{0\text{-}2hr}$ after breakfast; 2) maximum allowable missing interval – no interval greater than 20 minutes between non-missing measures for the outcome variables using ≤ 2-hour of CGM data (including $iAUC_{0\text{-}1hr}$, $iAUC_{0\text{-}2hr}$, average glucose excursions 0-1 or 0-2 hours and time in ranges 0-1 or 0- 2 hours after breakfast), and 25 minutes for other by-meal outcome variables.

The definition and derivation of these variables are described in detail in 9.1.

Table ITSI.6.8. Outcome Measures of CGM DATA

Category	Endpoints	24-Hour	Daytime[1]	Nighttime[2]	Breakfast[3]
Interstitial Glucose Reduction Rate following a Correction Bolus via the Pump (mg/dl/min and mg/dl/)[4]					
	Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >180 mg/dL (10.0 mmol/L) to recovery (interstitial glucose ≤180 mg/dL)	across all non-meal-related correction doses via the pump			
	Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >180 mg/dL [10.0 mmol/L] and ≤250 mg/dL [13.9 mmol/L]) to recovery (interstitial glucose ≤180 mg/dL)	across all non-meal-related correction doses via the pump			

Category	Endpoints	24-Hour	Daytime[1]	Nighttime[2]	Breakfast[3]
	Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >250 mg/dL [13.9 mmol/L] and ≤300 mg/dL [16.7 mmol/L]) to recovery (interstitial glucose ≤180 mg/dL)	across all non-meal-related correction doses via the pump			
	Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >300 mg/dL (16.7 mmol/L) to recovery (interstitial glucose ≤180 mg/dL)	across all non-meal-related correction doses via the pump			
Incremental AUCs (iAUCs) after Meals					
	$iAUC_{0\text{-}1hr}$				x
	$iAUC_{0\text{-}2hr}$				x
Average Glucose Excursions					
	average glucose excursion 0 to 1 hours				x
	average glucose excursion 0 to 2 hours				x
Glucose in the Target Ranges					
	Duration (in minutes) and percentage of time with glucose values within target range 71 to 180 mg/dL [3.9 and 10.0 mmol/L], both inclusive	x	x	x	x[5]
	Duration (in minutes) and percentage of time with glucose values within target range 71 to 140 mg/dL [3.9 and 7.8 mmol/L], both inclusive	x	x	x	x[5]
	Duration (in minutes) and percentage of time with glucose values ≤180 mg/dL [10.0 mmol/L]	x	x	x	x[5]
Hypoglycemic Episodes					
	Duration (in minutes) and percentage of time with glucose values <50, <60, and ≤70 mg/dL of hypoglycemic episodes, defined as at least 10 consecutive minutes <50, <60, and ≤70 mg/dL [2.8, 3.3, and 3.9 mmol/L]	x	x	x	x[5]

Category	Endpoints	24-Hour	Daytime[1]	Nighttime[2]	Breakfast[3]
	Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of hypoglycemic episodes, defined as at least 10 consecutive minutes <50, <60, and ≤70 mg/dL [2.8, 3.3, and 3.9 mmol/L]	x	x	x	
Hyperglycemic Episodes					
	Duration (in minutes) and percentage of time with glucose values >180, >250, and >300 mg/dL [10.0, 13.9, and 16.6 mmol/L] and hyperglycemic episodes, defined as at least 10 consecutive minutes >180, >250, and >300 mg/dL [10.0, 13.9, and 16.6 mmol/L]	x	x	x	x[5]
	Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of hyperglycemic episodes, defined as at least 10 consecutive minutes >180, >250, and >300 mg/dL [10.0, 13.9, and 16.6 mmol/L]	x	x	x	
Daily CGM Data Summary					
	Average glucose level	x	x	x	
	Median glucose level	x	x	x	
Glucose Variability and Risk Assessment					
Within-Day	CV	x	x	x	
	SD	x	x	x	
	IQR	x	x	x	
	MAGE	x	x	x	
	LBGI: frequency and extent of low BG readings	x	x	x	
	HBGI: frequency and extent of high BG readings	x	x	x	
	BGRI = LBGI + HBGI: a measure of overall variability and risks of hypo- and hyperglycemia	x	x	x	

Category	Endpoints	24-Hour	Daytime[1]	Nighttime[2]	Breakfast[3]
Between-day	CV	x	x	x	
	SD	x	x	x	
	MODD	x	x	x	
Overall[6]	CV	x	x	x	
	SD	x	x	x	
	IQR	x	x	x	
	LBGI	x	x	x	
	HBGI	x	x	x	
	BGRI	x	x	x	
Highest Postprandial Glucose					
	Time from start of meal to the highest postprandial glucose level (minutes) within 3 hours after breakfast				x
	Highest postprandial glucose level within 3 hours after breakfast				x
Other					
	Duration (in minutes) of each individual hypoglycemic episode (defined as at least 10 consecutive minutes <50, <60, and ≤70 mg/dL [2.8, 3.3, and 3.9 mmol/L])	across all hypoglycemic episodes with duration at least 10 consecutive minutes			

Abbreviations: AUC = area under curve; BGRI = blood glucose risk index; CGM = continuous glucose monitoring; CV = coefficient of variation; HBGI = high blood glucose index; IQR = interquartile range; LBGI = low blood glucose index; MAGE = mean amplitude of glycemic excursions; MODD = mean of daily differences; SD = Standard deviation.

Note:

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

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

3 Breakfast is defined as the first "Carbs" event between 4 AM and 11 AM that is associated with an "Insulin" event within ±30 minutes.

4 All eCOA non-meal related correction doses excluding those confirmed as delivered via syringe for an unexplained hyperglycemia that leads to infusion set change, will be those delivered via the pump.

5 Time in ranges within 0-1 hour and 0-2 hours after breakfast

6 Overall variability refers to the variability calculated based upon all the CGM measurements collected across all valid days for each derivation period (e.g. 4-6 weeks relative to the start of each of the randomized treatment period).

To assess the glucose control over the course of approximately 72-hours of continuous insulin infusion, the duration and percentage of time in ranges (target, hypoglycemia or hyperglycemia)

and incremental AUCs after breakfast, will be derived based upon the CGM raw data collected on each of the infusion set catheter dwell days, including Day 1 (<0 and ≥24 hours), Day 2 (<24 and ≥48 hours) and Day 3 (<48 and ≥72 hours), and summarized by treatment group.

The glucose reduction rate and duration of each individual hypoglycemia episode will be analyzed by an MMRM model. The MMRM model will include the fixed effects of treatment, period, and sequence as fixed effects and patient as a random effect.

The glucose reduction rate and duration of each hypoglycemia episode will be analyzed by an MMRM model. The MMRM model will include the fixed effects of treatment, period, and sequence as fixed effects and patient as a random effect.

Hypoglycemia/hyperglycemia rates as measured by CGM data will be summarized for 30 days and 1 year / 100 years (hypoglycemia <50 mg/dl and hyperglycemia >300 mg/dl only). The rate of hypoglycemia and hyperglycemia will be compared between treatment groups using Wilcoxon signed-rank test.

The proportion of patients with at least 1 hypoglycemia/hyperglycemia event as measured by CGM data in each category (incidence) during a specific period after randomization will be analyzed using a generalized linear mixed model with options of the binomial distribution and logit link function with treatment, period, and sequence. The within-patient error will be modeled as an unstructured variance-covariance matrix. Prescott's exact test will be conducted as sensitivity analyses.

Other than that, all continuous variables (actual and change from baseline, if applicable) will be compared between LY900014 and insulin lispro at Week 6 using the MMRMs (Model 2) defined in Section 6.1.

In addition, the following standardized glucose summary reports from AGP will be generated, based upon the observed CGM measures during Weeks 4 to 6 of each randomized treatment period:

- 24-hour period at individual patient level
- 0-1 hours and 0-2 hours relative to breakfast starting time, excluding patients who have had the next Carb or Insulin event (if any is captured) at the treatment group level

6.13. Efficacy Analyses

The analyses described in Section 6.13 will include data collected prior to permanent discontinuation (i.e., last dose) of IP in each 6-week treatment period, for all randomized patients.

The longitudinal observations of actual and change from baseline in HbA1c during the 12-week treatment period will be summarized by period and by treatment sequence. HbA1c reflects patients' blood glucose control over the past 2-3 months and therefore there may be potential carryover effect from Period I to Period II. For this reason, no treatment comparison will be conducted.

Actual and change from baseline 1,5-AG values will be compared between LY900014 and insulin lispro using MMRM defined in Section 6.1.

6.14. Subgroup Analyses for Primary Endpoint

The following subgroups will be explored to evaluate consistency of treatment effects on the primary safety measure using data collected from the Safety Population excluding data that are collected while patients temporarily are off pump or off IP:

- Duration of CSII use (using the median as the cutoff)
- Region (US, OUS)
- Pump Model

In addition, the primary endpoint will be assessed in the subset of patients with HbA1c $\leq$ 8% level at entry.

Exploratory subgroup analyses or summaries of hypoglycemic event data on historical use of SmartGuard/Threshold Suspend (Yes, No) will also be conducted on the Safety Population.

Additional exploratory subgroup analyses may also be performed.

6.15. Interim Analyses and Data Monitoring

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

6.16. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' Non-SAEs are summarized: by treatment group, by MedDRA preferred term.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- For each SAE, these additional terms are provided for EudraCT:
    - the total number of occurrences causally related to treatment

  - the total number of deaths
  - the total number of deaths causally related to treatment.

- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may be excluded if a 5% threshold is chosen. Allowable thresholds include 0% (all events), 1%, 2%, 3%, 4%, and 5%.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

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

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

8. References

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9. Appendix 1

9.1. Derivation of CGM Variables

9.2. General Derivation Specifications

All CGM variables will be derived for each patient, for each time interval of each study period (lead-in, Period I and Period II), based upon the data from valid CGM session days (Section 6.12). For Period I and Period II, the variables will be derived for 0-4, 2-6 (interstitial glucose reduction rates only), 0-6, and 4-6 weeks relative to the start of each randomized treatment period, respectively.

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

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

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

Only readings collected from valid CGM days while patients are on pump and on IP, will be included in the derived.

9.3. Interstitial Glucose Reduction Rate following a Correction Bolus via the Pump

The interstitial glucose reduction rate (mg/dl per minute and mg/dl per minute per unit of insulin dose) within 4 hours following a non-meal-related correction dose via the pump will be calculated by dividing the interstitial glucose reduction by the time it takes to first recover (≤180 mg/dL) from hyperglycemia after the correction dose. The interstitial glucose reduction rate will also be analyzed by sub-intervals of interstitial glucose levels at the time of the non-meal-related correction bolus: 180 to 250, 250 to 300, and >300 mg/dL (10 to 13.9, 13.9 to 16.7, and >16.7 mmol/L). The interstitial glucose levels at the time of the non-meal-related correction bolus, is defined as the most recent interstitial glucose within 1 hour prior to the correction bolus.

The non-meal related correction boluses delivered by pump will be derived through the following steps:

- Step 1: pull all correction boluses captured in eCOA;
- Step 2: exclude those correction boluses delivered through syringe;

- Step 3: exclude those associated with the last prior SMBG within 1 hour ≤180 mg/dl and the last post SMBG within 2 hours increases from prior SMBG. These correction boluses should not have been reported as non-meal related;
- Step 4: remove duplicate correction boluses. If 2 correction boluses are reported for the exact same time, only 1 correction bolus will be included;
- Step 5: if within 4 hours a second correction bolus is given before recovery (≤180 mg/dl), only the first non-meal-related correction bolus time will be used and the data after the second correction bolus will be censored. If the glucose never recovered to ≤180 mg/dL within 4 hours before any other correction boluses are given, the glucose reduction rate will be calculated by dividing the greatest glucose reduction within 4 hours before any other correction bolus, by the time it took to reach this level.

9.4. Incremental Area under the Glucose Curve (iAUC)

$iAUC_{0\text{-}T}$ will be calculated as the average value of iAUC on all valid CGM days during that visit with sufficient data to calculate the $iAUC_{0\text{-}T}$ (Section 6.12). For each day, $iAUC_{0\text{-}T}$ will be calculated as the sum of areas of all individual trapezoids within the time frame according to the formula:

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

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

9.5. Average Glucose Excursions

Average glucose excursions 0 to 1 hours and 0 to 2 hours will be calculated by averaging all excursion values within 1 or 2 hours. Excursions will be derived by subtracting glucose values by the starting glucose concentration, which is the average of the CGM values in the time window [-19, 0] mins relative to the start of the meal (at most 3 ISIG glucose measures).

9.6. Glucose in Target Ranges, Hypoglycemia- or Hyperglycemia

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

For example, if a patient had a total of 135 observations with glucose values ≤70 mg/dL (3.9 mmol/L) out of a total of 3078 observations recorded during the 24-hour period across days for Visit 8, the percentage of time spent in hypoglycemia during the 24-hour period for this patient at Visit 8 will be calculated as 135/3078 = 4.4%. The duration (in minutes) with hypoglycemia (glucose value ≤70 mg/dL [3.9 mmol/L]) during the 24-hour period for this patient at Visit 8 will be calculated as the percentage times 1440, i.e., 135/3078*1440 = 63.2 minutes.

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

9.7. Hypoglycemic/Hyperglycemic Episodes

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

The number of distinct hypoglycemic episodes that start will be derived along with days of CGM use (Section 6.12) to calculate the rate of hypoglycemic episodes during a 24-hour period. For example, the rate of postprandial hypoglycemic episodes (≤70 mg/dL [3.9 mmol/L]), during the 24-hour period, will be calculated with the following steps:

- Step 1: identify all events as runs of 3 or more consecutive CGM values meeting the criterion, where the pre-marker glucose value (≤70 mg/dL[3.9 mmol/L]). Consecutive implies no gaps in time more than 6 minutes between measurements. Events will be identified without regard for the CGM level prior to the start of the Carb event.
- Step 2: Count the number of distinct events over the 24-hour period.
- Step 3: Calculate rate per month by multiplying count by 30/days of CGM use. Days of CGM use will be calculated as the number of observations during the 24-hour period divided by the observation supposed to be measured during the period (288 observations for the 24-hour period).

9.8. Glucose Variability

Glycemic variability will be evaluated using the notation below:

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

n represents the number of time points within the time period

k represents a day within a visit

m represents number of days CGM is performed at a visit

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

9.8.1. Within-Day Variability

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

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

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

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

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

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

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

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

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

where,

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

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

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

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

9.8.2. Between-Day Variability

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

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

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

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

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

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

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

9.8.3. Overall Variability

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

9.8.4. Risk for Hypo/Hyperglycemia

The low blood glucose index (LBGI) has been developed to quantitate both frequency and severity of hypoglycemia. The LBGI has been validated as a predictor of severe hypoglycemia,

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

The LBGI, HBGI, and blood glucose risk index (BGRI) will be derived for each day of a visit and for overall in the following steps:

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

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

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

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

Step 2: Compute BG risk for each reading

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

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

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

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

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

Step 3: Compute LBGI and HBGI

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

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

Step 4: Compute BGRI

$BGRI = LBGI + HBGI$

9.9. Daily CGM Data Summary

For daily CGM summary variables, first determine the values within each day, then average across days within a visit.

9.10. AUC

Area under the curve (AUC) during a period (24-hour, daytime, or nighttime) will be calculated using the standard linear trapezoidal method as defined previously in Section 9.4, by multiplying the sum of trapezoids by (the length of the period)/(the length of the period - total length of gaps that are not counted into the calculation of the AUC).

9.11. Highest Postprandial Glucose

9.11.1. Time to the highest postprandial glucose within 3 hours after Meals

Time from start of meal to the highest postprandial glucose level will be calculated as the time from start of meal to the maximum glucose value within 3 hours after meals, excluding the data from patients who have had the next Carb or Insulin event.

9.11.2. Highest Postprandial Glucose Level within 3 hours after Meals

Highest postprandial glucose level excursions within 3 hours after meals, will be calculated as the maximum glucose value during 0-3 hours after start of meal, excluding the data from patients who have had the next Carb or Insulin event.

9.12. Other

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