Protocol I8B-MC-ITRO (c)

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

NCT03830281

Approval Date: 8-Oct-2019

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

2015-005358-36 (EUDRA CTA)

## Confidential Information



LY900014

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

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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# 1. Synopsis

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

**Rationale:**
Rapid-acting insulins have been shown to have a more rapid onset of action compared with human insulin; however, the consensus is that they are not rapid enough to match carbohydrate absorption and many patients are unable to achieve optimal glycemic control.

An ultra-rapid-acting prandial insulin with pharmacokinetic (PK) and pharmacodynamic (PD) profiles that demonstrate faster absorption and onset of action, may better match carbohydrate absorption and lead to improved postprandial control. The time action profile of a rapid-acting insulin could be enhanced through the addition of excipients to an existing formulation to increase capillary blood flow and/or enhance vascular permeability. An ultra-rapid insulin would be useful in the treatment of type 1 diabetes (T1D) and type 2 diabetes (T2D) when delivered by multiple daily injections (MDIs), by continuous subcutaneous insulin infusion (CSII), and in the development of closed loop insulin delivery systems.

The aim of this study is to demonstrate that an ultra-rapid formulation of insulin lispro, LY900014, is noninferior to Humalog on glycemic control as measured by change from baseline to Week 16 in HbA1c in patients with T1D using CSII when bolus doses are delivered in a double-blind manner immediately prior to each meal via an insulin pump.

**Objective(s)/Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | |
| 1. To test the hypothesis that LY900014 is noninferior to Humalog on glycemic control ([NIM = 0.4% for HbA1c) in patients with T1D using CSII for 16 weeks | 1. Difference between LY900014 and Humalog in change from baseline to Week 16 in HbA1c |
| **Multiplicity Adjusted Objectives** | |
| 2. To test the hypothesis that LY900014 is superior to Humalog in controlling 1-hour postprandial glucose (PPG) | 2. Difference between LY900014 and Humalog in the 1-hour PPG (serum glucose measured 1 hour after the start of the meal) from a MMTT at Week 16 |
| 3. To test the hypothesis that LY900014 is superior to Humalog in controlling 2-hour PPG | 3. Difference between LY900014 and Humalog in the 2-hour PPG (serum glucose measured 2 hours after the start of the meal) from a MMTT at Week 16 |
| 4. To test the hypothesis that LY900014 is superior to Humalog on improving glycemic control (HbA1c) | 4. Difference between LY900014 and Humalog in change from baseline to Week 16 in HbA1c |

| | |
|---|---|
| 5. To test the hypothesis that LY900014 is superior to Humalog in the duration of time glucose values within target range 70 to 180 mg/dL (3.9 to 10.0 mmol/L), obtained from CGM use during 24-hour period | 5. Duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period, from each 14-day CGM session at Week 16 |
| 6. To test the hypothesis that LY900014 is superior to Humalog in the duration of time glucose values within target range 70 to 180 mg/dL (3.9 to 10.0 mmol/L), obtained from CGM use during daytime | 6. Duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to daytime (0600 hours to midnight), from each 14-day CGM session at Week 16 |
| **Other Secondary Objectives** | |
| 7. To compare LY900014 and Humalog with respect to the rate of severe hypoglycemic events | 7. Rate (events/ patient/100 years) of severe hypoglycemic events from baseline through Week 16 |
| 8. To compare LY900014 and Humalog with respect to the rate and incidence of documented postmeal hypoglycemia | 8. Rate (events/patient/year) and incidence (percent of patients with at least 1 event) of documented postmeal hypoglycemia within 1 and 2 hours after the start of the meal from baseline through Week 16 |
| 9. To compare LY900014 and Humalog with respect to the rate and incidence of documented hypoglycemia | 9. Rate (events/patient/year) and incidence (percentage of patients with events) of documented hypoglycemic events from baseline through Week 16 |
| 10. To compare LY900014 and Humalog with respect to 1,5-AG | 10. Change from baseline 1,5-AG values at Week 16 |
| 11. To compare LY900014 and Humalog with respect to 10-point SMBG profiles | 11. Change from baseline 10-point SMBG values at Week 16 |
| 12. To compare LY900014 and Humalog with respect to total, basal, and bolus insulin dose | 12. Change from baseline in bolus/total insulin dose ratio at Week 16 |
| 13. To compare LY900014 and Humalog with respect to the proportion of patients achieving HbA1c targets | 13. The proportion of patients with HbA1c <7% and ≤6.5% at Week 16 |
| 14. To compare LY900014 and Humalog with respect to the duration of time spent in hypoglycemic glucose ranges, obtained from CGM use | 14. Duration (in minutes) and percentage of time with glucose values <54 and <70 mg/dL (3.0 and 3.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes <54 and <70 mg/dL, from each 14-day CGM session at Week 16 |
| 15. To compare LY900014 and Humalog with respect to the duration of time spent in hyperglycemic glucose ranges, obtained from CGM use | 15. Duration (in minutes) and percentage of time with glucose values >180 and >250 mg/dL (10.0 and 13.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes >180 and >250 mg/dL, from each 14-day CGM session at Week 16 |

| | |
|---|---|
| 16. To compare LY900014 and Humalog with respect to the incidence and rate of pump occlusion alarms that lead to an unplanned infusion set change | 16. Rate (events/patient/30 days) and incidence (percent of patients with at least 1 event) of pump occlusion alarms that lead to an unplanned infusion set change from baseline through Week 16 |
| 17. To compare LY900014 and Humalog with respect to the incidence and rate of episodes of unexplained hyperglycemia that lead to an unplanned infusion set change | 17. Rate (events/patient/30 days) and incidence (percent of patients with at least 1 event of unexplained hyperglycemia > 300 mg/dL confirmed by SMBG that leads to an unplanned infusion set change from baseline through Week 16 |

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

**Summary of Study Design:**

Study I8B-MC-ITRO (ITRO) is a Phase 3, prospective, randomized, outpatient, multinational, multicenter, 2-treatment group, parallel, active-controlled, double-blind study conducted in adult patients with T1D currently using CSII therapy.

This study involves adult patients who have been diagnosed with T1D for at least one year, have been using CSII therapy without interruption for at least 6 months, and have an HbA1c value of ≥6.5% and ≤9.0% at screening. Patients must be using insulin lispro, insulin aspart, or insulin glulisine in their pumps.

**Treatment Groups and Duration:**

The study includes a 1-week screening period and a 2-week lead-in period, followed by a 16-week treatment period, and a 4-week safety follow-up period. In the 2 treatment groups, LY900014 and Humalog will be given as both bolus and basal insulin, bolus doses will be given immediately prior to each meal (0 to 2 minutes).

**Number of Patients:**

Numbers are approximate: 526 participants will be screened to achieve 420 randomized patients and 368 patients completing 16 weeks of treatment.

**Statistical Analysis:**

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

Efficacy analyses will be conducted on all randomized patients according to the treatment the patients are assigned. The analyses for the primary and multiplicity adjusted objectives will be performed for the efficacy estimand including data collected prior to permanent discontinuation of investigational product (IP) and for the intention to treat (ITT) estimand including all data collected through Week 16 regardless of IP use. When change from baseline is included as a response variable of analysis models, the patient will be included in the analysis only if a baseline and at least one post-baseline measurement are available.

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

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

For the US Food and Drug Administration (FDA) submission, the primary analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand (treatment regimen estimand) which will include all data collected regardless of IP use. The reference for each treatment group will be from the retrieved dropout patients who discontinue IP but have the measurement at the primary endpoint in the same treatment group. If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis, the reference will be changed to include all observed data from all randomized patients in the same treatment arm who complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog from the analysis of covariance (ANCOVA) analysis of change from baseline to Week 16 in HbA1c using all randomized patients.

For non-FDA submissions and publications, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog at Week 16 (Visit 13) from the mixed-effect model repeated measures (MMRM) analysis of change from baseline in HbA1c including data collected from all randomized patients prior to permanent discontinuation of IP through Week 16 (efficacy estimand).

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

Hypoglycemia rates will be summarized for periods of 1 year and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical method. For each of the other categories of hypoglycemia, the number of hypoglycemia events during a specific period (rate) after randomization (for example, 0- to 4 weeks of treatment period) will be analyzed by using a negative binomial regression model including treatment. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days will be included in the model to estimate the rate of hypoglycemia per year. The proportion of patients with at least 1 hypoglycemic event in each category (incidence) during a specific period after randomization will be analyzed using a logistic regression model including treatment.

Similarly, a negative binomial model and a logistic regression model including treatment will be used to analyze the rate of pump occlusion alarms leading to unplanned infusion set changes per 30 days, and the proportion of patients with at least 1 occlusion alarm (incidence) leading to unplanned infusion set changes, respectively.

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

Change from baseline to last-observation-carried-forward endpoints for European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L) and ITSQ will be analyzed using ANCOVA models.

# 2. Schedule of Activities

**Table ITRO.1. Schedule of Activities**

| Study Procedure | Study Screening | Lead-In Period | | Treatment Period | | | | | | | | | | Safety Follow-up | ED |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **eCRF Visit Number** | **1** | **2** | **3** | **4** | **5[a]** | **6** | **7[a]** | **8** | **9** | **10** | **11** | **12** | **13** | **801** | **ED[b]** |
| **Visit Window (± days)** | | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **7** | **7** | **7** | **7** | **7** | **7** | |
| **Time on Study Relative to First Active Treatment Dose (weeks)** | **-3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **12** | **14** | **16** | **20** | |
| **Study Logistics** | | | | | | | | | | | | | | | |
| Informed consent signed | X | | | | | | | | | | | | | | |
| IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient eligibility review | X | | | | | | | | | | | | | | |
| Randomization[c] | | | | X | | | | | | | | | | | |
| **Clinical Assessments** | | | | | | | | | | | | | | | |
| Patient demographics | X | | | | | | | | | | | | | | |
| Medical history and preexisting conditions | X | | | | | | | | | | | | | | |
| Physical examination/height | X | | | | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events and product complaints | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body weight[d] | X | X | | | | X | | | | X | | | X | | X |
| Vital Signs: blood pressure/pulse rate[e] | X | X | | | | X | | | | X | | | X | | X |
| ECG[f] (12-lead) | X | | | | | | | | | | | | | | |
| **Patient Education and Management** | | | | | | | | | | | | | | | |
| Diabetes and nutritional counseling | | X | | | | | | | | | | | | | |
| Transfer to Humalog[g] | | X | | | | | | | | | | | | | |
| Record model of pump used in the eCRF | X | | | | | | | | | | | | | | |
| Record use of low glucose suspend[h] | X | | | | | | | | | | | | | | |
| Record low sensor glucose alert limit(s) | | X | X | X | | X | | X | X | X | X | X | X | | X |
| Record model of infusion set type used in the eCRF | X[i] | | | | | | | | | | | | | | |

| Study Procedure | Study Screening | Lead-In Period | | Treatment Period | | | | | | | | | | Safety Follow-up | ED |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **eCRF Visit Number** | **1** | **2** | **3** | **4** | **5[a]** | **6** | **7[a]** | **8** | **9** | **10** | **11** | **12** | **13** | **801** | **ED[b]** |
| **Visit Window (± days)** | | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **7** | **7** | **7** | **7** | **7** | **7** | |
| **Time on Study Relative to First Active Treatment Dose (weeks)** | **-3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **12** | **14** | **16** | **20** | |
| Record pump bolus delivery speed in the eCRF: 630G and 640G (standard or quick speed); 530G, Paradigm Revel, and Paradigm Veo (only standard speed) | X | | | | | | | | | | | | | | |
| Train on routinely changing the reservoir and infusion set every 3 days (may repeat as needed) | | X | | | | | | | | | | | | | |
| **Patient Education and Management** | | | | | | | | | | | | | | | |
| Assist patient to connect the study BG meter to their pump and select the option "Always" send BG results to pump | | X | | | | | | | | | | | | | |
| Assist patient to set a pump reminder to prompt for a reservoir and infusion set change every 3 days | | X | | | | | | | | | | | | | |
| Site staff to verify synchronization of the dates and times of pump and BG meter | | X | X | X | | X | | X | X | X | X | X | X | | |
| Change infusion set and reservoir at investigative site[j] | | X | | X | | | | | | | | | X | | |
| Remind patients to change infusion set and reservoir the evening prior to MMTT | | | X | | | | | | | | | X | | | |
| Review pump basal rates and bolus calculation factors and adjust as needed[k] | | X | X | X | X | X | X | X | X | X | X | X | | | |
| Train on collecting glucose (4-, 7-, and 10-point) profiles[l] | | X | | | | | | | | | | | | | |
| Review 4-point glucose profiles[m] | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Remind patient of 7-point glucose profiles[n] | | X | | | X | | | | X | | | | | | |
| Review 7-point glucose profiles[m] | | | X | | | X | | | | X | | | | | |

| Study Procedure | Study Screening | Lead-In Period | | Treatment Period | | | | | | | | | | Safety Follow-up | ED |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **eCRF Visit Number** | **1** | **2** | **3** | **4** | **5[a]** | **6** | **7[a]** | **8** | **9** | **10** | **11** | **12** | **13** | **801** | **ED[b]** |
| **Visit Window (± days)** | | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **7** | **7** | **7** | **7** | **7** | **7** | |
| **Time on Study Relative to First Active Treatment Dose (weeks)** | **-3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **12** | **14** | **16** | **20** | |
| Remind patient of 10-point SMBG profile requirements[o] | | X | | | | X | | | | | | X | | | |
| Review 10-point SMBG | | | | X | | | | X | | | | | X | | |
| Train/remind patient on CGM to record date and start time of all meals and bedtime snack, if consumed, in patient diary during blinded CGM sessions | | X | X | | | | | | X | | | X | | | |
| Insert CGM sensor, attach transmitter and pair with receiver[p] | | X | | | | | | | X | | | X | | | |
| Site staff to verify the date and time of the Dexcom G5 Receiver; adjust if needed | | X | | | | | | | X | | | X | | | |
| Remind patient to change CGM sensor every 7 days | | X | X | | | | | | X | | | X | | | |
| **Patient Education and Management** | | | | | | | | | | | | | | | |
| Remove CGM sensor and detach transmitter | | | | X[q] | | | | | | X | | | X[q] | | |
| Remind patient to avoid the use of acetaminophen/paracetamol during CGM use | | X | X | | | | | | X | | | X | | | |
| Upload CGM data to Study Management Suite[r] | | | | X | | | | | | X | | | X | | |
| Start nonstudy rapid-acting insulin and reset pump to basal rates and bolus calculator settings used at randomization | | | | | | | | | | | | | X | | X |
| Dispense Study Diary | | X | X | X[s] | | X[s] | | X | X | X | X | X | X | | |
| Review and collect study diary for clinical decision making | | | X | X | | X | | X | X | X | X | X | X | X | X |
| **IP and Ancillary Supplies** | | | | | | | | | | | | | | | |

| Study Procedure | Study Screening | Lead-In Period | | Treatment Period | | | | | | | | | | Safety Follow-up | ED |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **eCRF Visit Number** | **1** | **2** | **3** | **4** | **5[a]** | **6** | **7[a]** | **8** | **9** | **10** | **11** | **12** | **13** | **801** | **ED[b]** |
| **Visit Window (± days)** | | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **7** | **7** | **7** | **7** | **7** | **7** | |
| **Time on Study Relative to First Active Treatment Dose (weeks)** | **-3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **12** | **14** | **16** | **20** | |
| Dispense blood glucose meter and complete training [l] | | X | | | | | | | | | | | | | |
| Dispense blood glucose meter supplies[t] | | X | | X | | X | | X | X | X | X | X | X | | |
| Dispense pump infusion sets, reservoirs and other ancillary supplies | | X | | X | | X | | X | X | X | X | X | X | | |
| Dispense CGM sensors to complete 14-day sessions (2x) | | X | | | | | | | X | | | X | | | |
| Dispense IP | | X | | X | | X | | X | X | X | X | X | | | |
| Drug accountability | | | | X | | X | | X | X | X | X | X | X | | X |
| Collect used and unused study drug | | | | X | | X | | X | X | X | X | X | X | | X |
| Return CGM transmitter and receiver | | | | X | | | | | | X | | | X | | |
| **Transfer Diary Data to eCRF and Discuss with Patient [u]** | | | | | | | | | | | | | | | |
| Hypoglycemia events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 10-point SMBG | | | | X | | | | X | | | | | X | | X[v] |
| Unplanned infusion set changes with noted reason(s) | | | X | X | | X | | X | X | X | X | X | X | | X |
| Planned infusion set changes | | | X | X | | X | | X | X | X | X | X | X | | X |
| Urine Ketone results if available | | | X | X | | X | | X | X | X | X | X | X | X | X |
| Recorded dates and start times of meals and bedtime snacks (if consumed) during blinded CGM sessions | | | | X | | | | | | X | | | X | | |
| **Transfer Pump Data to eCRF** | | | | | | | | | | | | | | | |
| Total daily basal and total daily bolus insulin doses (3 days prior to visits) | | X | | X | | X | | X | | X | | | X | | X |
| Bolus calculator settings: ISF, CR, AIT | | X | X | X | | X | | X | X | X | X | X | X | X | X |

| Study Procedure | Study Screening | Lead-In Period | | Treatment Period | | | | | | | | | | Safety Follow-up | ED |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **eCRF Visit Number** | **1** | **2** | **3** | **4** | **5[a]** | **6** | **7[a]** | **8** | **9** | **10** | **11** | **12** | **13** | **801** | **ED[b]** |
| **Visit Window (± days)** | | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **7** | **7** | **7** | **7** | **7** | **7** | |
| **Time on Study Relative to First Active Treatment Dose (weeks)** | **-3** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **12** | **14** | **16** | **20** | |
| Number of each bolus type used: normal, square or dual wave during the 7 days prior to visit | | | | X | | | | | | | | | X | | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | |
| Patient fasts prior to visit | | | | X | | | | | | | | | X | | |
| MMTT[w] | | | | X | | | | | | | | | X | | |
| Record the basal rate at the start of the MMTT and if it changes during the MMTT | | | | X | | | | | | | | | X | | |
| Urinalysis panel | X | | | | | | | | | | | | | | |
| Pregnancy test[x] | X | | | X | | | | | | | | | | | |
| Follicle-stimulating hormone test[y] | X | | | | | | | | | | | | | | |
| Chemistry panel | X | | | | | | | | | | | | X | | X |
| eGFR | X | | | | | | | | | | | | | | |
| Hematology | X | | | | | | | | | | | | X | | X |
| 1.5-Anhydroglucitol | | | | X | | | | X | | X | | | X | | X |
| **Laboratory Assessments** | | | | | | | | | | | | | | | |
| Hemoglobin A1c | X | | | X | | | | X | | X | | | X | X | X |
| Anti-insulin lispro antibodies | | | | X | | | | | | | | | X | X | X |
| **Health Outcomes Questionnaires[z]** | | | | | | | | | | | | | | | |
| ITSQ | | X | | X | | | | | | | | | X | | X |
| EQ-5D-5L | | X | | X | | | | | | | | | X | | X |

Abbreviations: AIT = active insulin time; CF = correction factor; CGM = continuous glucose monitoring; CR = carbohydrate ratio; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life – 5 Dimensions 5 Level; IP = investigational product; ISF = insulin sensitivity factor; ITSQ = Insulin Treatment Satisfaction Questionnaire; IWRS = interactive web-response system; MMTT = mixed meal tolerance test; SMBG = self-monitored blood glucose.

a Telephone visits are indicated by shaded columns.

b Patients who have been randomized will be asked to return for the ED visit in a fasting state unless patient is already fasting and at the site when the decision to discontinue is made. Patients who discontinue during the lead-in period prior to randomization who are not already at the site will be asked to return for the ED in a nonfasting state and all activities should be completed except for laboratory tests and questionnaires.

c Randomization should occur after all Visit 4 procedures including MMTT. If MMTT is rescheduled post Visit 4, randomization should not occur until baseline MMTT is completed. The patient will administer their first dose of study insulin with the first meal after the MMTT has been completed and randomization has occurred.

d Patients should be advised to remove their shoes/coats and empty their pockets before the body weight is obtained.

e Vital sign measurements must be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. These measurements should be determined after patients have been seated quietly for at least 5 minutes in a chair with feet on the floor. The arm used for blood pressure measurement should be supported at heart level.

f Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

g Only for patients using insulin glulisine or insulin aspart.

h Low glucose suspend is referred to as “Threshold Suspend” (530G), “Low Glucose Suspend” (Paradigm Veo), or “Suspend on low” (630G and 640G).

i Record infusion set model and cannula length if changed during the study.

j Reservoir is filled with Humalog at lead-in (Visit 2), IP at randomization (Visit 4), and prestudy insulin at end of treatment (Visit 13).

k During the lead-in period, basal rates and bolus settings should be evaluated and adjusted if needed. During the treatment period, basal rates and bolus settings should be titrated in order to meet the target BG levels.

l Training may be repeated at other visits, as needed.

m Glucose profiles may be obtained from download of device software (CareLink, Dexcom, and Freestyle Libre). Patient will be responsible for entering glucose values into pump for bolus calculation and to review with investigator. Four- and 7-point profiles are needed for clinical management only.

n Patients should be instructed to perform two 7-point glucose profiles within the week prior to the 3 Visits. The 7-point profile is completed over a 1-day period, preferably on 2 nonconsecutive days (weekdays and weekends).

o Patients should be instructed to perform three 10-point SMBG profiles within the 2 weeks prior to the 3 visits. The 10-point profile is completed over a 1-day period, preferably on 2 nonconsecutive days (weekdays and weekends) using the study blood glucose meter.

p Sensors will need to be changed every 7 days during each CGM session. One receiver will be used for all 3 sessions. Two transmitters will be supplied; one for Sessions 1 and 2 and one for Session 3. Transmitter and receiver will be stored at site between sessions.

q At Visits 4 and 13, remove sensor and transmitter following the completion of the MMTT.

r Sites to check data acceptability reports following upload to confirm no major time gaps occurred during each data capture session. Continuous glucose monitoring collection time gaps greater than 3 hours may require further investigation or re-training.

s At Visits 4 and 6, provide an extra diary for the telephone Visits 5 and 7.

t Glucose monitoring supplies will be dispensed at other visits, as needed.

u Diary data should be discussed at telephone visits and transferred to the eCRF at subsequent office visits.

v Review of 7- and 10-point SMBG profiles at the ED visit will take place only for patients randomized into the study.

w MMTT can occur 0 to 4 days prior to the visit and patient must be fasting prior to start of the MMTT. The patient should change their infusion set the evening prior to the MMTT.

x Serum pregnancy test at Visit 1, urine pregnancy test at Visit 4 prior to IP exposure, and at other times at the investigator's discretion. When required per local regulations and/or institutional guidelines, local pregnancy testing will occur at mandatory times during the study treatment period.

y Follicle-stimulating hormone test must be performed at Visit 1 for a postmenopausal woman who is between 50 and 54 years of age (inclusive) with an intact uterus, not on hormone therapy and has had at least 6 months of spontaneous amenorrhea.

z Health outcomes questionnaires will be administered at the study sites based on the availability of appropriate translations. The questionnaires should be administered prior to other study procedures.

# 3. Introduction

## 3.1. Study Rationale

Rapid-acting insulins have been shown to have a more rapid onset of action compared with human insulin; however, the consensus is that they are not rapid enough to match carbohydrate absorption and many patients are unable to achieve optimal glycemic control.

An ultra-rapid-acting prandial insulin with pharmacokinetic (PK) and pharmacodynamic (PD) profiles that demonstrate faster absorption and onset of action, may better match carbohydrate absorption and lead to improved postprandial control. The time action profile of a rapid-acting insulin could be enhanced through the addition of excipients to an existing formulation to increase capillary blood flow and/or enhance vascular permeability. An ultra-rapid insulin would be useful in the treatment of type 1 diabetes mellitus (T1D) and type 2 diabetes mellitus (T2D) when delivered by multiple daily injections (MDIs), by continuous subcutaneous insulin infusion (CSII), and in the development of closed loop insulin delivery systems.

The aim of this study is to demonstrate that an ultra-rapid formulation of insulin lispro, LY900014, is noninferior to Humalog on glycemic control as measured by change from baseline to Week 16 in HbA1c in patients with T1D using CSII when bolus doses are delivered in a double-blind manner immediately prior to each meal via an insulin pump.

## 3.2. Background

LY900014 is comprised of the active ingredient, insulin lispro, as well as 2 excipients (treprostinil and citrate) that facilitate rapid absorption of insulin lispro into the blood stream. This novel formulation results in earlier glucose lowering when compared with Humalog. This faster glucose lowering response, as demonstrated by the PK and PD profiles of LY900014 when compared with Humalog, more closely mimics the time–action profile of normal endogenous insulin secretion. This enhanced activity is expected to provide greater glycemic control as dosing relative to the start of a meal can be reduced when compared with the timing required for the currently available rapid-acting insulin analogs. Dosing closer to the start of a meal will allow patients to better match the needed insulin dose to the carbohydrate content of their meal.

## 3.3. Benefit/Risk Assessment

In Phase 1 clinical studies, the assessment of AEs, hypoglycemic events, local tolerability, vital signs, physical examination, electrocardiogram (ECG), anti-insulin lispro antibodies, and clinical laboratory assessments did not reveal any specific risks of LY900014 beyond those already known for Humalog. LY900014 has been well tolerated in both healthy subjects and patients with diabetes mellitus. Notably, there have been no clinically significant increases in adverse events (AEs) associated with systemic absorption of treprostinil (headache, diarrhea, nausea, jaw pain, vasodilatation, rash, edema, and hypotension are described in the Remodulin prescribing information, 2014). Plasma treprostinil concentrations were all below the lower limit of quantitation after subcutaneous (SC) administration of LY900014.

Because insulin pump therapy uses only rapid-acting insulin, the onset of diabetic ketoacidosis (DKA) can occur quickly if insulin delivery is interrupted. Diabetic ketoacidosis develops when insulin levels are insufficient to meet the body's basic metabolic requirements. Diabetic ketoacidosis is an acute metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. Signs and symptoms may include vomiting, abdominal pain, deep gasping breathing, increased urination, weakness, confusion, and occasionally loss of consciousness. There has been one report of DKA in completed studies of LY900014. A high blood glucose (BG) that is not responding to a correction bolus via insulin pump may indicate an infusion set occlusion or insulin pump problem. Patients in the current study will be provided with guidance about the management of high BG, including provision of urine ketone strips, in the setting of possible infusion set occlusion or insulin pump malfunction. Patients will also be provided with insulin syringes as an alternate method of investigational product (IP) delivery in the event of pump malfunction and disruption.

In Phase 1 clinical studies, LY900014 has consistently demonstrated a faster time–action profile than Humalog. In patients with T1D or T2D treated with MDI insulin therapy, LY900014 significantly reduced postprandial glucose (PPG excursions compared with Humalog when both were dosed by syringe at the start of a test meal. Two studies in patients with T1D have been completed using CSII in an in-patient setting, both of which have demonstrated accelerated time action.

More detailed information about the known and expected benefits and risks of Humalog may be found in the country-specific product labeling (for example, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics). The Investigator's Brochure (IB) describes the clinical and nonclinical development of LY900014.

Safety evaluation in this study will include hypoglycemia, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), frequent glucose monitoring, frequent visits, provision of urine ketone test strips for hyperglycemia troubleshooting, blood pressure, and body weight. More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY900014 can be found in the IB.

# 4. Objectives and Endpoints

Table ITRO.2 shows the objectives and endpoints of the study.

**Table ITRO.2. Objectives and Endpoints**

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

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

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

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

# 5. Study Design

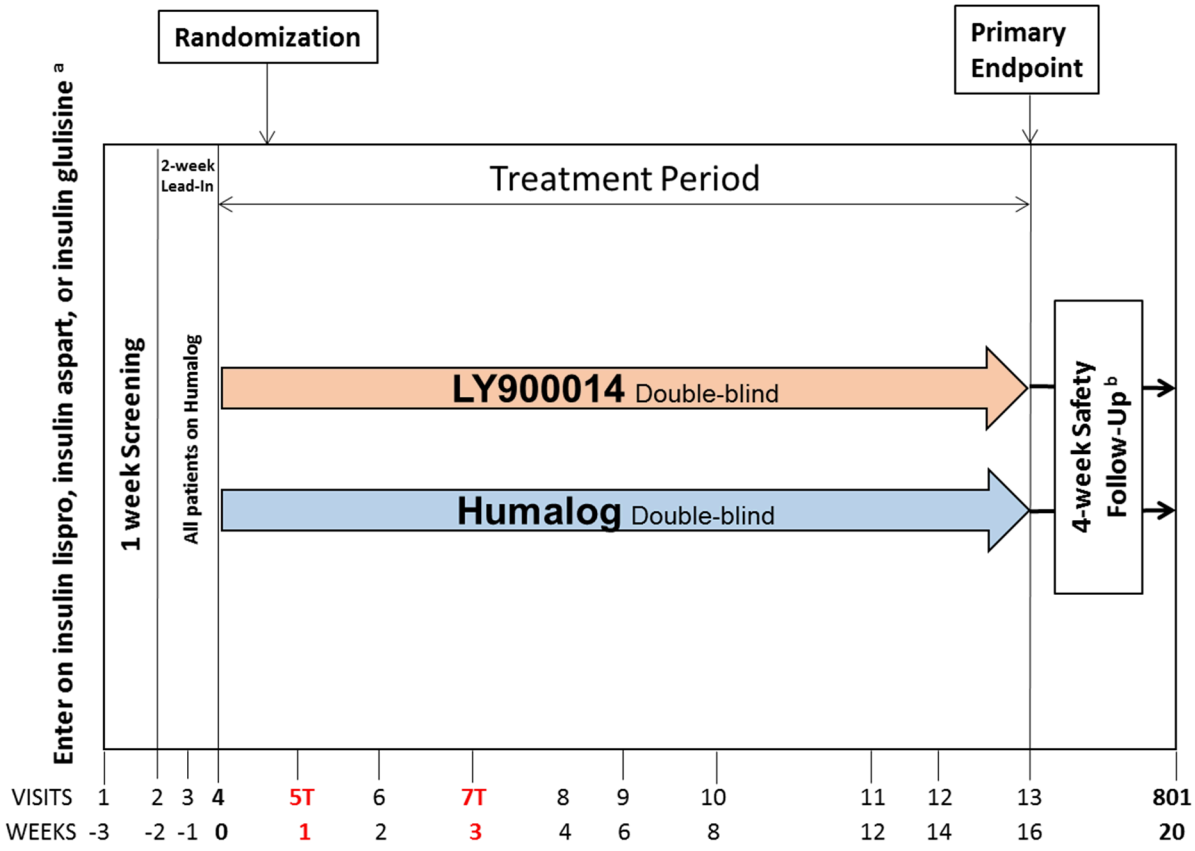
## 5.1. Overall Design

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

Patients treated with a rapid-acting insulin analog—insulin lispro, insulin aspart, or insulin glulisine via CSII—will be eligible for inclusion in the trial. All patients will use Humalog during the lead-in period. Those treated with either insulin aspart or insulin glulisine at screening will be transferred to Humalog at Visit 2. At Visit 4, patients will be randomized to either LY900014 or Humalog with bolus doses given immediately prior to each meal.

Specific elements of this study design will include collection of 10-point self-monitored blood glucose (Section 9.1.4.2), blinded continuous glucose monitoring (CGM) sessions (Section 9.1.4.6), and Mixed Meal Tolerance Testing (Section 9.1.4.7.).

Study governance considerations are described in detail in Appendix 3. Figure ITRO.1 illustrates the study design.




Abbreviation: T=Telephone Visits.

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

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

**Figure ITRO.1. Illustration of study design for Clinical Protocol I8B-MC-ITRO.**

## 5.2. Number of Participants

Numbers are approximate: 526 participants will be screened to achieve 420 randomized and 368 patients completing 16 weeks of treatment.

## 5.3. End of Study Definition

End of the study is the last scheduled procedure shown in the Schedule of Activities (Section 2, Table ITRO.1.) for the last patient.

### *5.3.1. Safety Follow-up*

Safety follow-up visit guidelines are as follows (see Section 2, Table ITRO.1.):

- Patients who discontinue from the study during the lead-in period (prior to randomization), only need to complete an early discontinuation visit.
- Patients who discontinue from IP early will be encouraged to remain in the study and complete all remaining visits per the Schedule of Activities, including Visit 801.
- Patients who discontinue from the study early (regardless of whether they discontinue IP at the same time or have discontinued IP at an earlier visit), should complete an early discontinuation visit followed by the safety follow-up visit as per the Schedule of Activities.
- Patients who finish Visit 13 without early discontinuation of IP should complete a safety follow-up visit (Visit 801) 4 weeks after Visit 13.

## 5.4. Scientific Rationale for Study Design

Study ITRO is a Phase 3 study to evaluate LY900014 compared with Humalog when given by CSII in patients with T1D. The study has 2 treatment groups, both of which are double-blind to allow comparison of LY900014 and Humalog when bolus doses are given immediately prior to the start of each meal.

The primary endpoint of this study is designed to compare HbA1c lowering. HbA1c is a validated measure of glycemic control over time and is the best marker for development and progression of diabetes complications. HbA1c is widely accepted by health care providers (HCPs) and regulatory authorities.

During the 2-week lead-in period, the following will occur:

- perform the first 14-day blinded CGM session,
- assess patient proficiency in carbohydrate counting and provide training, and
- assess basal rates and bolus calculator settings and adjust if needed.

During the 16-week treatment period, the following should be titrated in order to meet the target BG levels:

- pump basal rates
- bolus calculator settings
    - carbohydrate ratios (CR),
    - insulin sensitivity factors (ISF), and
    - active insulin time (AIT)

## 5.5 Justification for Dose

The basal and bolus delivery of insulin will be determined based on the individual needs of each patient. LY900014 has the same insulin lispro concentration (100 U/mL) as that of commercially available Humalog. At the randomization visit, IP may be substituted for Humalog (used during lead-in) on a unit-for-unit basis. The addition of treprostinil to the

Humalog formulation does not modify the physical, chemical, or biological integrity of Humalog. Furthermore, the total glucose-lowering effect during euglycemic clamp experiments is similar between LY900014 and Humalog. Nevertheless, improved postprandial glucose values were observed with LY900014 after test meals, which may potentially increase the risk for early postprandial hypoglycemia with LY900014.

# 6. Study Population

Patients must give written informed consent (approved by Eli Lilly and Company [Lilly] or its designee and the ethical review board [ERB] governing the site) before being allowed to participate in the study and before any screening assessments are performed.

Study investigator(s) will review the patient's records and/or history and screening test results/measurements to determine if the patient meets all inclusion and no exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the patient begins the lead-in period.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

## 6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

**Type of Patient and Disease Characteristics**

[1] Men or women diagnosed (clinically) with T1D for at least 1 year prior to screening, and continuously using insulin for at least 1 year

**Patient Characteristics**

[2] Are at least 18 years of age

[3] Have HbA1c values of ≥6.5% and ≤9.0%, as determined by the central laboratory at screening (Visit 1)

[4] Have a body mass index (BMI) of ≤35.0 kg/$m^2$ at screening (Visit 1).

[5] Male patients:

a. No male contraception required except in compliance with specific local government study requirements

[6] Female patients:

a. Women not of childbearing potential may participate and include those who are:

i. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis;

*Or*

ii. postmenopausal – defined as either

1. a woman 50 to 54 years of age (inclusive) with an intact uterus, not on hormone therapy who has had either

    a. cessation of menses for at least 1 year;

    *Or*

    b. at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL;

    *Or*

2. a woman 55 years of age or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea;

    *Or*

3. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

b. Women of childbearing potential participating:

i. Cannot be pregnant or intend to become pregnant

ii. Cannot be breastfeeding (including the use of a breast pump)

iii. Must remain abstinent or use 1 highly effective method of contraception or a combination of 2 effective methods of contraception for the entirety of the study (See Appendix 5)

iv. Test negative for pregnancy at the time of screening (Visit 1). Note: a urine pregnancy test is conducted at Visit 4.

[7] Have refrigeration in the home or have ready access to refrigeration for storage of insulin

[8] Are a patient for whom the investigator has determined can be randomized and maintain the treatment regimens based on their previous medical history including insulin dosing regimens, hypoglycemic episodes, and glycemic control

**Treatment Characteristics**

[9] Currently treated with <100 Units of one of following rapid-acting analog insulin via CSII for at least the last 30 days prior to screening;

a. insulin lispro U-100,

b. insulin aspart,

c. fast-acting insulin aspart (where approved), or

d. insulin glulisine

[10] Have been using CSII therapy for a minimum of 6 months prior to screening. Interruption of CSII is allowed during the 6 months prior to screening for up to a total of 14 days, such as during a hospitalization, a pump malfunction, or a "pump holiday."

[11] Must be using a MiniMed 530G (US), Paradigm Revel (US), MiniMed 630G (US and Canada), MiniMed 640G or Paradigm Veo (in select countries outside the US), insulin pump for at least the last 90 days and are capable of and willing to

a. stay on the same pump throughout the study

b. use study-provided MiniMed insulin pump reservoirs and infusion sets

c. maintain their current bolus delivery speed (standard or quick) for the duration of the study

d. use carbohydrate counting for meal-related bolus dosing

e. use the pump's bolus calculator (Bolus Wizard®), including entry of the current glucose value, to determine mealtime and correction bolus doses

[12] May be wearing a Medtronic CGM using the "Threshold Suspend" (530G), "Low Glucose Suspend" (Paradigm Veo) "Suspend on low" (630G and 640G), and/or "Suspend before low" (640G) pump feature. Beginning with the lead-in period (Visit 2) patients must be willing to;

a. continue "Threshold Suspend" (530G), "Low Glucose Suspend" (Paradigm Veo) or "Suspend on low" (630G or 640G) for the duration of the lead-in and treatment periods

b. stop "Suspend before low" (640G) for the duration of the lead-in and treatment periods.

[13] May be using personal CGM or FGM to self-monitor glucose at study entry.

a. If chooses to continue, must be willing to maintain its use for the duration of the study.

b. May not begin use of personal CGM or FGM during the study.

[14] Are capable of, and willing, to do the following:

a. Perform 10-point self-monitored blood glucose (SMBG), prior to designated visits (patients using a personal CGM or flash glucose monitoring (FGM) device must perform 10-point SMBG with study provided glucose meter)

b. Perform 4- and 7-point glucose profiles prior to designated visits

c. Adhere to a routine infusion set and reservoir change interval of every 3 days

d. Avoid use of all products containing acetaminophen or paracetamol while using the study-provided Dexcom CGM

e. Keep records in patient study diaries required by this protocol

f. Receive diabetes education

g. Comply with required study treatment and study visits

**Informed Consent**

[15] Have given written informed consent to participate in this study in accordance with local regulations

## 6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

**Medical Conditions**

[16] Have any other condition (including known drug or alcohol abuse or psychiatric disorder including eating disorder) that precludes the patient from following and completing the protocol

[17] Have hypoglycemia unawareness as judged by the investigator

[18] Have had more than 1 episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) within 6 months prior to screening

[19] Have had more than 1 emergency room visit or hospitalization due to poor glucose control (hyperglycemia or DKA) within 6 months prior to screening

[20] Have cardiovascular disease, within the last 6 months prior to screening, defined as stroke, decompensated heart failure New York Heart Association class III or IV (CCNYHA 1994), myocardial infarction, unstable angina pectoris, percutaneous transluminal coronary angioplasty or coronary arterial bypass graft

[21] Renal:

a. History of renal transplantation
b. Currently receiving renal dialysis
c. Serum creatinine >2.0 mg/dL (177 μmol/L) at screening, or
d. An estimated glomerular filtration rate of <30 mL/min/1.73 $m^2$.

[22] Hepatic: have obvious clinical signs or symptoms of liver disease (for example, acute or chronic hepatitis, or cirrhosis), or elevated liver enzyme measurements as indicated below at screening:

a. Total bilirubin level (TBL) ≥2X the upper limit of normal (ULN) (with the exception of Gilberts Disease) as defined by the central laboratory,

*Or*

b. Alanine aminotransferase (ALT) ≥3X ULN as defined by the central laboratory,

*Or*

c. Aspartate aminotransferase (AST) ≥3X ULN as defined by the central laboratory

[23] Malignancy: have active or untreated malignancy, have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years, or are at an increased risk for developing cancer or a recurrence of cancer in the opinion of the investigator

[24] Have any hypersensitivity or allergy to any of the insulins or excipients used in this trial

[25] Hematologic: have had a blood transfusion or severe blood loss within 90 days prior to screening or have known hemoglobinopathy, anemia that is clinically significant based on investigator judgement, or any other traits of known to interfere with measurement of HbA1c

[26] Have presence of clinically significant gastrointestinal disease (for example, clinically active gastroparesis associated with wide glucose fluctuations; includes those with gastric bypass) in the opinion of investigator

[27] Have significant lipohypertrophy, lipoatrophy, or scars within the SC tissue in areas of infusion, in the opinion of the investigator

[28] Have a history of abscess at an infusion site within the last 90 days prior to screening

[29] Have vision loss or hearing loss that does not allow recognition of pump screens, alerts and alarms

**Prior/Concomitant Therapy**

[30] Have used insulin human inhalation powder (Afrezza®) within 30 days prior to screening

[31] Are receiving any oral or injectable medication intended for the treatment of diabetes other than rapid-acting analog insulin via CSII in the 90 days prior to screening. In the event of interruption of CSII ≤14 days during the 6 months prior to screening, injection of bolus and basal insulin is allowed.

[32] Glucocorticoid therapy: are receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (including intravenous (IV), intramuscular (IM), SC, and oral), but excluding topical, intraocular, intranasal, intra-articular, and inhaled preparations), or have received such therapy within 4 weeks immediately prior to screening with the exception of replacement therapy for adrenal insufficiency

**Prior/Concurrent Clinical Trial Experience**

[33] Are currently enrolled in any other clinical trial involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study

[34] Have participated, within the last 30 days in a clinical trial involving an IP

[35] Have previously completed or withdrawn from this study or any other study investigating LY900014 after receiving at least 1 dose of the IP

**Other Exclusions**

[36] Have an irregular sleep/wake cycle (for example, patients who sleep during the day and work during the night)

[37] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[38] Are Lilly employees (including employees, temporary contract workers, or designees responsible for the conduct of the study)

### *6.2.1. Rationale for Exclusion of Certain Study Candidates*

The use of LY900014 in pediatric patients (<18 years of age) will be studied separately. This study will specifically examine comparison of LY900014 to Humalog in adult patients using CSII. Criterion [2] defines the population age for the purpose of this study. Therefore, pediatric patients are excluded.

## 6.3. Lifestyle Restrictions

Patients should be instructed not to donate blood or blood products during the study. Patients should be instructed to avoid major changes in diet or exercise during the study. Patients should be instructed to avoid all medications that contain acetaminophen/paracetamol during the blinded CGM study sessions. Patients should be instructed to avoid major changes in dietary intake or physical activity during the 3 days prior to mixed meal tolerance test (MMTT).

## 6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, with the exception of individuals from select countries who initially screen failed because they use a Paradigm Revel or Paradigm Veo pump. Retests are also not allowed, except for cases when results are unavailable from the original sample.

# 7. Treatments

## 7.1. Treatments Administered

This study involves a double-blind comparison of LY900014 and Humalog, in patients with T1D using CSII. Table ITRO.3 shows the treatment regimens.

**Table ITRO.3. Treatment Regimens**

| Regimen | Dose Strength | Dose Administration | Route of Administration | Timing of Dose |
|---|---|---|---|---|
| LY900014 | 100 U/mL | Individualized Dosing | CSII | Mealtime bolus 0-2 min prior to start of the meal; continuous basal infusion; correction boluses as necessary |
| Humalog | 100 U/mL | Individualized Dosing | CSII | Mealtime bolus 0-2 min prior to start of the meal; continuous basal infusion; correction boluses as necessary |

Abbreviation: CSII = continuous subcutaneous insulin infusion.

The investigator or his or her designee is responsible for the following:

- explaining the correct use of IP to the patient
- explaining storage requirements for IP
- explaining requirements for recording time and amount of bolus doses to the patient
- maintaining accurate records of IP dispensing and collection
- at the end of the study returning all used and unused IP to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

### *7.1.1. Packaging and Labelling*

Clinical trial materials will be labeled as IP as appropriate, and according to the regulatory requirements of the country. Study insulins (LY900014 and Humalog) will be supplied by Lilly or its representative, in accordance with current good manufacturing practices and will be supplied with lot numbers.

The blinded vials will contain a concentration of 100 U/mL in 10-mL vials of either LY900014 or Humalog.

During the lead-in period, Humalog 100 U/mL will be provided in open-label 10-mL vials.

### *7.1.2. Insulin Pumps*

Patients will use their personal insulin pumps for the duration of the study but will be required to use reservoirs and infusion sets provided by the investigative site. Pump reservoirs will be filled

with IP and infusion sets will be primed according to the manual of use provided by the pump manufacturer. Patients will be required to change the insulin, reservoir, and infusion set every 3 days, routinely throughout the study, in accordance with the label of the infusion sets. Sites should assist patients with setting a reminder in their pump to prompt for a reservoir and infusion set change every 3 days.

If a pump malfunction requires a patient to change to a new insulin pump during the study, it will be allowed as long as the new pump

- is approved in the country where the patient resides
- is allowed by the study (MiniMed 530G, Paradigm Revel, 630G, Paradigm Veo or 640G)
- Training has been provided to the patient by a qualified HCP, and
- is compatible with a Contour Link blood glucose meter that
    - is approved in the country where the patient resides and
    - can be sourced by the Sponsor for the Study.

#### 7.1.2.1. Personal Continuous Glucose Monitor Use in Study

Patients may continue to use their personal CGM or FGM during the study.

Patients will not be allowed to start using personal CGM or FGM during the study. In order to account for potential differences between patients who wear a CGM or FGM and those who do not, stratification by patients' personal CGM or FGM use will ensure balance of this factor across treatments. Patients may use their personal CGM or FGM for the required glucose value entries into the pump bolus calculator for meal and correction boluses, if approved in their country for making treatment decisions (i.e., nonadjunctive use). Patients will be required to perform SMBG with the study provided blood glucose meter for the study procedures described in Section 9.1.4.3.

### *7.1.3. Medical Devices*

Study patients will be provided with an approved, compatible blood glucose meter. The patient's meter must be wirelessly connected to their insulin pump. Instructions for connecting are found in the pump and meter user guides and also provided as a site tool. Once connected, the pump automatically controls the date and time of the meter. It will also send all BG results directly to the pump when the "Always" meter send option is selected (recommended). The BG meters used in this study will be have received clearance from the Food and Drug Administration (FDA) and meet the following standard for blood glucose meters: ISO 15197:2013. At every site visit beginning with Visit 2, site staff should verify synchronization of the dates and times of the pump and BG meter.

## 7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 4. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign all vials containing double-blind IP during the study and open-label Humalog during the lead-in

period. Site personnel will confirm that they have located the correct vials by entering a confirmation number found on the vials into the IWRS.

Patients will be randomized to 1 of 2 treatment groups in 1:1 ratio. Stratification will be by country, HbA1c stratum (≤7.5%, >7.5% at Visit 1), and patient's personal CGM or FGM use during the study (yes/no).

Patients will begin using double-blind IP in their pumps immediately following successful completion of the Visit 4 MMTT. Patients will fill a new pump reservoir and infusion set with IP, then insert a new pump infusion set cannula and begin infusion of IP prior to leaving the investigative site.

## *7.2.1. Selection and Timing of Doses*

### 7.2.1.1. Target Glucose Values for Titration of Insulin Therapy

The overall glycemic control goals for all patients enrolled in the study are similar to those recommended by the American Association of Clinical Endocrinologists (AACE) (Bailey et al. 2016). Fasting, prandial, bedtime, and peak PPG target values used to reach the glucose targets and for determination of titration in insulin therapy are listed in Table ITRO.4

**Table ITRO.4. Target Glucose Values for Titration of Insulin Therapy**

| Time of Measurement | Target (Range) |
|---|---|
| Fasting or pre-morning meal | Target: 100 mg/dL or 5.6 mmol/L<br>Range: 80 to <100 mg/dL or 4.4 to 6.1 mmol/L |
| Pre-midday meal | Target: 100 mg/dL or 5.6 mmol/L<br>Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L |
| Pre-evening meal | Target:100 mg/dL or 5.6 mmol/L<br>Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L |
| Pre-bedtime and 03:00 AM | Range: 90 to 130 mg/dL or 5.0 to 7.2 mmol/L |
| 1-2-hour postprandial | Target: <180 mg/dL or 10.0 mmol/L |

### 7.2.1.2. Pump Settings

Evaluating and titrating pump settings is at the discretion of the investigator and should be done with a methodical approach by reviewing relevant glucose data, insulin delivery settings and carbohydrate intake. During titration of pump settings, patients should eat meals that have known carbohydrate content and can be accurately counted and avoid snacking between meals (unless treating hypoglycemia). Patients will be allowed to use low glucose suspend for the lead-in and duration of the treatment period. Patients will not be allowed to use "SmartGuard Suspend before low" (Refer Section 6.1 Inclusion Criteria [12]).

### 7.2.1.3. Basal Rate Titration

At all clinic and telephone visits during the 16-week treatment period following randomization, titration of basal rates should be based on glucose values, hypoglycemia data and determined by the investigator in discussion with the patient. Additional discussion between visits may be

required to enable the patient to reach the fasting blood glucose target of 100 mg/dL (5.6 mmol/L) and to optimize 24-hour basal rates. Titration of basal rates may be influenced by other clinical circumstances and safety considerations known to the investigator; thus, the prescribed basal rates during the study are determined by, and the responsibility of, the investigator.

Overnight basal rates should be assessed by observing patterns across time segments (bedtime to mid-sleep; mid-sleep to awakening) and titrated to match diurnal variations. When basal rates are set correctly, patients should be able to sleep late, eat late, or skip a meal without experiencing glucose excursions.

Daytime basal rates can be titrated using either the fasting method or nonfasting method.

If using the fasting method, evaluate glucose levels across skipped-meal time segments (pre-morning to pre-midday, pre-midday to pre-evening, or pre-evening to bedtime) and titrate/add basal rate(s) based on the patterns observed across skipped-meal times.

If using the nonfasting method, evaluate basal rates by comparing the 2-hour postmeal glucose to the next premeal glucose. Postmeal glucose should steadily decline and return to premeal target range by next meal.

#### 7.2.1.4. Bolus Dose Titration

Postprandial glucose levels from 10-point SMBG profiles and 7-point glucose profiles should be evaluated by the investigator for titration of bolus dosing. Additional glucose testing should be considered during the days following transition to study insulin. Titration of bolus calculator settings (CR, ISF, and AIT) during the study are determined by, and the responsibility of, the investigator.

Patients should use the pump Bolus Wizard® calculator for calculating bolus and correction doses to ensure that the carbohydrate content of each meal is covered and the preprandial glucose level is accounted for in the preprandial bolus dose.

In order to meet the target glucose levels during the 16-week treatment period, the investigator in discussion with the patient should;

- Weekly assess and titrate the CR, ISF, and AIT
    - The CR is used to calculate food bolus amounts. Evaluate CRs by comparing the pre-meal glucose to its corresponding 2-hour post-meal glucose. The CR may be titrated every 3-4 days (twice per week) when appropriate, based on the patient's glycemic needs and glucose levels.
    - The ISF is used to calculate correction bolus amounts that is needed to bring the glucose into target range.

- Weekly discuss and determine optimal bolus types (normal, square or dual wave) for meals of different macronutrient composition. For meals that tend to be larger in size and of higher protein and fat content (often the dinner meal), a higher bolus dose or a dual or square wave bolus may be appropriate to prevent late postmeal hyperglycemia.

#### 7.2.1.5. Transitioning off Study Prandial Insulin Therapy

Patients will give their last bolus dose of study insulin (LY900014 or Humalog) at Visit 13 with the MMTT or at early discontinuation. No special instructions are necessary for patients who were randomized to either LY900014 or Humalog. After completion of study treatment, patients will restart the rapid-acting insulin analog used prior to study entry via CSII and their pumps settings will be reset to those used at randomization.

## 7.3. Blinding

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

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

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

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

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

## 7.4. Dosage Modification

See Section 7.2.1.

## 7.5. Preparation/Handling/Storage/Accountability

The investigator or his or her designee is responsible for confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive IP, and only authorized site staff may supply or administer study treatment. All study treatments should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

All insulin products must be stored at the investigative site under refrigerated conditions (between 2°C and 8°C) in a locked and secure place. Insulin must not be frozen.

Vials of insulin not currently in-use should be refrigerated until ready to use. In-use insulins should be maintained at room temperature (between 20°C and 25°C) when possible and refrigerated material should be warmed to near room temperature before infusion. In-use insulin must not be used after 28 days.

The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

## 7.6. Treatment Compliance

The investigator or designee will assess compliance of the patient at each visit, based on a review of the patient's glycemic control, adherence to the visit and treatment schedule, and completion of the patient's study diary. Patients who are deemed noncompliant will receive additional diabetes education and training, as required, and the importance of compliance with the protocol will be reinforced. Patients who, in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from IP.

## 7.7. Concomitant Therapy

The following concomitant medications

- are NOT allowed at any time during the study;
    - Any noninsulin diabetes treatment therapy
    - Afrezza® (inhaled insulin)
- Are NOT allowed during the blinded CGM sessions;
    - Medicines containing Acetaminophen/paracetamol
- ARE allowed for up to a total of 7 days during the lead-in period and 14 days during the treatment period;
    - Systemic glucocorticosteroids
        - IV, IM, SC, oral
            - except in the case of replacement therapy for adrenal insufficiency
- ARE allowed for 14 days or less during the study
    - Basal insulin

- Regular human insulin or a nonstudy rapid-acting analog insulin

- ARE allowed at any time
  - Topical, inhaled, intraocular, intra-articular, or intranasal steroid preparations

## 7.8. Treatment after the End of the Study

### *7.8.1. Treatment after Study Completion*

LY900014 will not be made available to patients after conclusion of the study. Rapid-acting insulin analogs and regular human insulin are available in all countries for use as prandial/pump insulin.

### *7.8.2. Special Treatment Considerations*

After discontinuation of IP at the end of the treatment period or earlier, randomized patients should restart the rapid-acting analog insulin used prior to study entry.

Investigators should provide patients with appropriate guidance for glucose monitoring and insulin dose adjustment throughout the follow-up period in order to maintain glycemic control.

# 8. Discontinuation Criteria

## 8.1. Discontinuation from Study Treatment

In the event that a patient is discontinued from the study treatment, the investigator should encourage the patient to remain in the study for continued safety monitoring.

Lilly recognizes the importance of complete data collection. This study includes elements to minimize missing data. Patients who are discontinued from IP before study completion are encouraged to remain in the study for continued monitoring. For patients who remain in the study after early discontinuation of IP, both efficacy (HbA1c) and safety data will be collected at scheduled visits. The difference between stopping IP and discontinuing the study will be explained to patients as part of the informed consent, and patients will be encouraged to continue in the study even if they stop study drug. In addition, study site investigators will be trained on the importance of complete data collection, with additional re-education of sites and patients as necessary.

### *8.1.1. Permanent Discontinuation from Study Treatment*

Patients will be discontinued from the IP in the following circumstances:

- The investigator may decide that the patient should stop IP. If this decision is made because of an AE, SAE, or a clinically significant laboratory value, the study drug is discontinued for that patient and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately.
- The patient may decide to stop IP.
- If the patient becomes pregnant.
- If an investigator, study site personnel performing assessments, or patient is unblinded, the patient must discontinue IP.
- If the patient, for any reason, requires treatment with another therapeutic regimen or therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from IP should occur prior to introduction of the new agent.
- Use of prohibited concomitant medication (Guidance on restrictions for concomitant therapies is provided in Section 7.7).
- Use of pump that is not allowed.
- If the patient has not used IP for more than 14 days total.
- If the patient experiences a second episode of severe hypoglycemia

**Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from IP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via case report form (CRF).

Discontinuation of the IP for abnormal liver tests **should be considered** by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor.

- ALT or AST >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients discontinuing from the IP prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities Table ITRO.1.), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

### *8.1.2. Temporary Discontinuation from Study Treatment*

Patients can have temporary discontinuation of IP for up to a total of 14 days (consecutive or nonconsecutive).

In the event of a pump failure, MDI therapy is allowed for ≤14 days. Bolus and basal insulin will be determined by the investigator or other HCP. When possible, continuing on IP is preferred. Investigational product may be withdrawn from the vial and injected as needed to cover meals and correct hyperglycemia using the insulin syringes provided.

### *8.1.3. Discontinuation of Inadvertently Enrolled Patients*

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with IP. Safety follow-up is as outlined in Section 2 (Schedule of Activities Table ITRO.1.), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

## 8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include the following:

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- The investigator decides to discontinue the patient from the study
- The patient requests to be discontinued from the study
- The patient discontinues Humalog regimen for >3 consecutive days in the lead-in period

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities Table ITRO.1.), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol. Patients who discontinue during the lead-in period will not need to fast, have laboratory tests drawn, or complete questionnaires, but will have all other early discontinuation procedures performed. Site should document details regarding the reason for discontinuation when available.

## 8.3. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Due diligence efforts should be documented in electronic case report form (eCRF).

# 9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities (Table ITRO.1.), with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

## 9.1. Efficacy Assessments

### *9.1.1. Primary Efficacy Assessments*

The primary efficacy measure is the change from baseline to Week 16 in HbA1c.

### *9.1.2. Secondary Efficacy Assessments*

The following secondary efficacy measures will be collected at the times shown in the Schedule of Activities (Section 2).

- Fasting and PPG collected during the MMTT:
  - 1-hour and 2-hour PPG: serum glucose measured 1 hour and 2 hours after the start of the meal
  - Incremental areas under the serum glucose concentration-time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after a meal; maximum serum glucose after a meal
  - Glucose variability measured by the coefficient of variation and standard deviation (SD)
- 1,5-Anhydroglucitol (1,5-AG)
- SMBG 10-point profiles:
  - 1-hour and 2-hour PPG and PPG excursions by meal and across all meals
  - Within- and between-day glucose variability measured by the coefficient of variation and SD
- CGM
  - Duration and percentage of time in range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime (0600 hours to midnight) and 24-hour period obtained by study-provided Dexcom blinded CGM
  - Duration and percentage of time with glucose values <54 and <70 mg/dL (3.0 and 3.9 mmol/L)

  - Duration and percentage of time with glucose values >180 and >250 mg/dL (10.0 and 13.9 mmol/L)

- Proportion of patients with HbA1c ≤6.5% and <7.0%
- Bolus, basal and total insulin dose (units and units/kg) and bolus/total insulin ratio

### *9.1.3. Appropriateness of Assessments*

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to diabetes.

### *9.1.4. Study Procedures*

The following procedures will be performed at the times shown in the Schedule of Activities (Section 2).

#### 9.1.4.1. Use of Personal CGM or FGM

Patients may continue to use their personal CGM or FGM throughout the study (Section 7.1.2.1). Patients will be allowed to use their personal CGM/FGM for the 4- and 7-point glucose profiles (as consistent with local regulations and standard of care), and then enter the sensor glucose values into their pump. If patients do not have a personal CGM/FGM, they will be required to perform the 4- and 7-point glucose profiles using the study provided BG meter and these glucose values will be automatically transferred to the pump. The 4-and 7-point values are required at the times described in Table ITRO.5.

#### 9.1.4.2. Collection of Glucose Profiles

Patients will be asked to collect 4-, 7-, and 10-point glucose profiles according to Table ITRO.5. The 4- and 7-point profiles are needed for clinical management. The 10-point profile will be required for a study endpoint. The 10-point must be collected using the study BG meter. Site personnel may request additional glucose values at other times to make clinical management decisions. Missing values in any glucose or SMBG profile will not be considered protocol deviations unless, in the opinion of the investigator, they are excessive and reflect noncompliance with the protocol.

During the 10-point SMBG profiles, patients should be encouraged to eat meals in the morning, midday, and evening (and eat a snack if that is their usual practice).

**Table ITRO.5. Collection Schedule for Glucose Profiles**

| Glucose Profile | How Many | When |
|---|---|---|
| 4 Points | Daily | Daily |
| 7 Points | 6 total | 2x during week prior to Visits 3, 6, and 10 |
| 10 Points | 9 total | 3x during the 2 weeks prior to Visits 4, 8, and 13 |

| | Glucose Profile | | |
|---|---|---|---|
| Time Point | 4 Points | 7 Points | 10 Points (SMBG) |
| Fasting [pre-morning meal] | X | X | X |
| 1 hour post-morning meal | | | X |
| 2 hour post-morning meal | | X | X |
| pre-midday meal | X | X | X |
| 1 hour post-midday meal | | | X |
| 2 hour post-midday meal | | X | X |
| pre-evening meal | X | X | X |
| 1 hour post-evening meal | | | X |
| 2 hour post-evening meal | | X | X |
| Bedtime | X | | X |
| 03:00 AM | | X | |

Abbreviation: SMBG = self-monitored blood glucose.

### 9.1.4.3. Use of Study Provided Blood Glucose Meter

The Study SMBG meter must be used to

- Collect 10-point SMBG profiles (Table ITRO.5)
- Confirm hypoglycemia events (glucose value ≤70 mg/dL)
- Confirm all hyperglycemia events (glucose value >300 mg/dL
- Calibrate the Dexcom CGM every 12 hours during blinded CGM sessions
- Test SMBG at the time of each unplanned infusion set change for any reason

### 9.1.4.4. Infusion Set Changes

Patients will be expected to routinely fill a new pump reservoir with study drug and insert a new infusion set into an appropriate SC site every 3 days during the study. Patients will be required to enter all reservoir and infusion set changes (planned and unplanned) into their study diary, including the date and time and reason for the change. Reasons for unplanned changes are;

- a pump occlusion alarm,
- an unexplained hyperglycemia,
- an infusion site reaction, or
- an infusion set problem.

For each unplanned infusion set change, SMBG (and urine ketone test, if indicated) should be performed and entered into the study diary.

#### 9.1.4.5. Urine Ketone Testing

Patients will be provided urine ketone testing strips for use in hyperglycemia management. It is recommended that patients test for urine ketones and record in Patient Diary when;

- SMBG is >300 mg/dL,
- nausea, vomiting, or abdominal pain is present,
- an illness occurs.

If moderate or large amounts of urine ketones are present, patients should notify the investigator immediately and go to the Emergency Room.

#### 9.1.4.6. Blinded Continuous Glucose Monitoring Sessions

The Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5) will be used by all patients in blinded mode 14 days prior to Visits 4, 10, and 13. The Dexcom G5 is an FDA-approved and European Union European Conformity (CE) labelled device, developed for continuous monitoring of interstitial glucose levels in persons with diabetes mellitus. Prior to each blinded CGM session, site staff should verify the date and time of the Dexcom G5 Receiver and adjust if needed. Patients will be instructed to change the Dexcom G5 sensor every 7 days according to the product label. Patients will receive training on the use of the Dexcom G5 and will be expected to complete daily requirements.

Patients will need to consider the second 7-day end time of the baseline and endpoint sensor sessions so that they are able to continue to wear the blinded CGM during both MMTTs. If the second sensor is scheduled to end on the day of the MMTT, the patient should end the sensor session and insert a new sensor the evening prior to the scheduled time of the MMTT.

**Daily Requirements for Patients during each Blinded Dexcom G5 Session**

- Eat a similar breakfast each day and avoid snacking for the 2-hour period after breakfast unless it is necessary to treat hypoglycemia.
- Enter date and start time of all meals into the Patient Diary
- Enter date and start time of bedtime snack, if consumed, into the Patient Diary
- Keep the Dexcom G5 Receiver close to the body
    - within about 6 meters (about 20 feet) of the Dexcom G5 Transmitter,
    - without obstruction, to minimize the loss of transmitted data.
- Calibrate the Dexcom G5 Sensor every 12 hours.
    - Use SMBG values taken only from finger-sticks for calibrations.
    - Do not use alternative BG site testing (forearm, palm, etc.) for sensor calibration.
- Avoid products containing acetaminophen/paracetamol while using the Dexcom G5.

### 9.1.4.7. Mixed Meal Tolerance Test

**A 4-hour MMTT will be performed in all patients at**

- baseline (Week 0, Visit 4) and
- the end of the treatment period (Week 16, Visit 13).

**The MMTT <u>can</u>**

- occur 0 to 4 days prior to Visit 4 or Visit 13, but as close to the Visit date as possible.
- be rescheduled up to 2 times within the visit window, ideally at 24-hour intervals, if the patient does not meet the target FBG.
- occur after a non-severe hypoglycemic episode is recorded within the 8-hour fasting period and up to 2 hours prior to the test meal if it is treated and resolved with 20 grams or less of carbohydrate

**The MMTT <u>cannot</u> occur**

- if a correction bolus dose was given less than 4 hours before the start of the test meal.
- if non-severe hypoglycemic episode during the 8-hour fasting period and up to 2 hours prior to the start of test meal requires more than 20 grams of carbohydrate, or
- if patient has an episode of severe hypoglycemia within the past 24 hrs.

**The day prior to the MMTT, patients will be instructed to**

- follow normal eating and exercise routines
- refrain from intake of alcohol

**The evening prior to the MMTT, patients will be instructed to**

- fast for at least 8 hours prior to scheduled testing
- fill a new pump reservoir and infusion set
    - with open-label Humalog - Visit 4
    - with IP - Visit 13
- insert a new infusion set into an appropriate site

**The morning of scheduled MMTT, patients will be instructed to**

- measure SMBG at 4 AM
    - This SMBG value should be used by patients to evaluate the need for a correction bolus or the intake of no more than 20 grams of carbohydrate to arrive at the investigator site with a BG between 71 and 180 mg/dL prior to the MMTT.
- keep programmed basal rates
- continue to wear the CGM device until the end of the MMTT

- if the sensor session is scheduled to end on the day of the MMTT, the patient should end the sensor session and insert a new sensor the evening prior to the scheduled time of the MMTT.

**Target FBG**

Patients should have a FBG in the range of 71 to 180 mg/dL (4.0 to 10.0 mmol/L) prior to starting the MMTT.

**Test Meal**

- The test meal (approximately 700 kcal and 100 grams of carbohydrate) will consist of 2 cans of Ensure Plus®, Abbott Nutrition.
- Patients are expected to consume the meal within 15 minutes.
- Patients should consume the same test meal for both the baseline and end of primary treatment period MMTT.

**Insulin Infusion**

The morning meal CR will be used to calculate the bolus dose for the MMTT, adjusting if needed for the fat content of the test meal. A supplemental correction dose based on the patient's ISF may be added to the bolus if the glucose is above the fasting or pre-meal target.

All patients will have a bolus dose given 0 to 2 minutes prior to the start of the meal.

- With open-label Humalog - Visit 4
- With IP - Visit 13

**Sample Collection**

Time 0 of the MMTT will be when the patient starts to consume the meal. Serial venous blood samples to measure serum glucose will be taken at time -15, 0, 15, 30, 60, 120, 180, and 240 minutes after the start of the meal.

**Hypoglycemia during the MMTT**

| If the patient | Then the patient should |
|---|---|
| has signs or symptoms of hypoglycemia during the MMTT | have BG measured with the site-provided Point of Care BG meter. |
| has BG ≤70 mg/dL (3.9 mmol/L) | receive 15 g of rapidly absorbable oral carbohydrate and repeat BG testing after 15 min or as clinically indicated. |
| has a repeated BG that is still ≤70 mg/dL (3.9 mmol/L) | receive another 15 g of carbohydrate until BG is >70 mg/dL (3.9 mmol/L). |
| reaches a BG >70 mg/dL (3.9 mmol/L) | continue the sample collection of the MMTT per the schedule |

Abbreviations: BG = blood glucose; MMTT = mixed meal tolerance test.

#### 9.1.4.8. Diabetes Education and Nutritional Counseling

Initial training at Visit 2 will include diabetes education and nutrition counseling. Patients may be provided additional training and education at visits following Visit 2, based on individual needs. Appropriate site personnel will provide training and education using locally approved diabetes education/training materials and programs or by using other materials that may be provided by the sponsor.

Training will include reviews of:

- correct pump use
    - 3-day frequency of routine reservoir and infusion set changes,
    - priming of the infusion set,
    - infusion site rotation,
    - use of temporary basal rates and alternate bolus types
- carbohydrate counting,
- calculating bolus and correction doses, and
- treating hypoglycemia.
- managing hyperglycemia

## 9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for all AEs through an appropriate health care option. All AEs will be followed until restoration or until a stable condition has been achieved. The follow-up should not be interrupted, even if there is a reasonable explanation for the event.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, IP, via electronic data entry.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the IP, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

### *9.2.1. Serious Adverse Events*

An SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- When a condition related to the pump necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.
- Severe hypoglycemia events: Episodes of severe hypoglycemia as determined by the investigator according to the definition provided in Section 9.4.1 and Section 9.4.2 must be reported as SAEs

All AEs occurring after signing the ICF are recorded in the CRF. The SAE reporting begins after the patient has signed the ICF and has received IP. However, if an SAE occurs after signing the ICF, but prior to receiving IP, the SAE should be reported to the sponsor according to SAE-reporting requirements and timelines if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the CRF.

Pregnancy (during maternal or paternal exposure to IP) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

#### 9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

### *9.2.2. Complaint Handling*

Lilly collects product complaints on IPs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP or their insulin pump so that the situation can be assessed. Any insulin pump issue will be assessed at the investigative site and if not resolved, the investigator should report the complaint directly to the pump manufacturer in accordance with the product labeling. Investigators should report these complaints as they would for products in the marketplace.

- Complaints on IP must be reported to Lilly by site staff within 24 hours of notification, or within 24 hours of study/site personnel becoming aware of a product issue, regardless of the availability of the complaint sample.
- Investigative sites must retain the IP under appropriate storage conditions, if available or when obtained, until instructed to return it to Lilly.
- Product complaints for Non-Lilly Products (including concomitant drugs and insulin pumps) that do not have a Lilly Product Batch or Control number are reported directly to the manufacturer per product label.

- Follow the instructions outlined in the Product Complaint Form for other reporting requirements.

## 9.3. Treatment of Overdose

Excess insulin administration may result in hypoglycemia. Refer to the IB for LY900014 and product label for Humalog.

## 9.4. Safety

### *9.4.1. Hypoglycemia*

Patients will be required to perform SMBG when hypoglycemia is suspected through

- symptoms experienced,
- personal CGM or FGM readings, or
- a perceived increased risk as related to
    - dietary intake,
    - physical activity, or
    - inadvertent or atypical insulin dosing.

All patients will be instructed to treat a BG ≤70 mg/dL (3.9 mmol/L) as hypoglycemia.

If a hypoglycemia event is suspected, the patient should record the BG value, any associated symptoms, and the treatment administered in the study diary. The patient should contact the site as necessary. All hypoglycemia events (severe and nonsevere) must be reported on the hypoglycemia eCRF. All episodes of severe hypoglycemia must be confirmed by the investigator and then reported as SAEs on the AE eCRF page and on the SAE eCRF page. Episodes of hypoglycemia not meeting the criteria for severe hypoglycemia should not be reported as an AE.

Hypoglycemia will be described using the following definitions:

- **Documented Glucose Alert; BG ≤70 mg/dL (3.9 mmol/L):**
    - Documented symptomatic hypoglycemia: an event with typical symptoms of hypoglycemia.
    - Documented asymptomatic hypoglycemia: an event without typical symptoms of hypoglycemia.
    - Documented unspecified hypoglycemia: with no information about symptoms of hypoglycemia available (this has also been called unclassifiable hypoglycemia).
- **Documented Clinically Significant Hypoglycemia with similar criterion as above except for threshold BG <54 mg/dL (3.0 mmol/L)**
    - Documented symptomatic hypoglycemia

- Documented asymptomatic hypoglycemia
- Documented unspecified hypoglycemia

- **Probable Symptomatic Hypoglycemia**: an event during which symptoms are present, but BG measurement was not reported.
- **Severe Hypoglycemia**: during these episodes, patients have an altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and the event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG ≤70 mg/dL [3.9 mmol/L]).
- **Other Hypoglycemia**
  - **Nocturnal Hypoglycemia:** any documented hypoglycemic event (including severe hypoglycemia) that occurs between bedtime and waking.
  - **Overall (or Total) Hypoglycemia**: this category combines all cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia) excluding the events of relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category.

### *9.4.2. Severe Hypoglycemia*

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based upon the medical need of the patient to have required assistance and is not predicated on the report of a patient simply having received assistance.

### *9.4.3. Electrocardiograms*

For each patient, an ECGs should be performed at Visit 1 according to the study-specific requirements described in the Schedule of Activities (Section 2, Table ITRO.1.).

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

ECGs may be obtained at additional times, when deemed clinically necessary.

### 9.4.4. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2, Table ITRO.1.) including the study-specific requirements.

### 9.4.5. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2, Table ITRO.1.).

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of IP should be reported to Lilly or its designee as an AE via electronic data entry.

### 9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

#### 9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

**Hepatic Safety Data Collection**

Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- Elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- Elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- Patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE

## 9.5. Pharmacokinetics

Not applicable

## 9.6. Pharmacodynamics

Not applicable

## 9.7. Pharmacogenomics

Not applicable

## 9.8. Immunogenicity Testing

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro as specified in the Schedule of Activities (Section 2, Table ITRO.1).

Immunogenicity will be assessed by a validated radio ligand-binding assay (RBA) to detect anti-insulin lispro antibodies in the presence of lispro. Instead of quantitating the level of anti-insulin lispro antibodies by titer, the RBA reports a semiquantitative percent-binding for each positive sample. Additionally, positive samples will be characterized for cross-reactive binding to native insulin.

Clinical and reliable on-market data indicate that the immunogenic potential of insulin lispro is comparable to other marketed insulins such as regular human insulin (Fineberg et al. 1996) and, when present, anti-insulin antibodies do not appear to be clinically consequential (Fineberg et al. 2003). Therefore, rather than relying on an in vitro neutralization assay, well established in vivo measures of insulin lispro efficacy (that is, insulin dose, HbA1c) will be utilized to directly monitor for any potential neutralizing effect of anti-lispro antibodies.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by Lilly or its designee. The duration allows the sponsor to respond to future regulatory requests related to LY900014.

## 9.9. Health Economics

The self-reported questionnaires will be administered according to the Schedule of Activities (Section 2, Table ITRO.1.) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

### *9.9.1. EQ-5D-5L*

The European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L) (van Reenen and Janssen [WWW]) is a patient-rated questionnaire used to evaluate health status. The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). This part of the EQ-5D can be used to generate a health state index score, which is often used to compute quality-adjusted life years for utilization in health economic analyses. The health state index score is calculated based on the responses to the 5 dimensions, providing a single value on a scale from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility. The second part of the questionnaire consists of a visual analog scale (VAS) on which the patient rates their perceived health state from 0 (worst imaginable health state/the worst health you can imagine) to 100 (best imaginable health state/the best health you can imagine).

### *9.9.2. Insulin Treatment Satisfaction Questionnaire*

The insulin treatment satisfaction questionnaire (ITSQ) (Anderson et al. 2004) is a validated instrument containing 22 items that assesses treatment satisfaction for persons with diabetes on insulin. Items are measured on a 7-point Likert scale, where lower scores reflect better outcomes. In addition to an overall score, the items that make up the 5 domains of satisfaction are categorized as:

- Inconvenience of Regimen (5 items)
- Lifestyle Flexibility (3 items)
- Glycemic Control (3 items)
- Hypoglycemic Control (5 items)
- Insulin Delivery Device Satisfaction (6 items).

All individual patient-domain scores will be calculated as the mean of nonmissing items in the domain if <20% of the items within the relevant domain are missing otherwise, the domain score will be missing. The domain scores will be transformed to a scale of 0-100 (derived as 100*[7-raw score]/6). An overall score is calculated as the mean of the nonmissing transformed domain score and only calculated when all 5 domain scores are nonmissing. A higher score indicates better treatment satisfaction.

# 10. Statistical Considerations

## 10.1. Sample Size Determination

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

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

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

## 10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Entered | All patients who give informed consent |
| Enrolled | All patients who receive at least 1 dose of open-label Humalog in the 2-week lead-in period |
| Randomized | All patients who are randomly assigned to study treatment at Visit 4.<br>Treatment group will be defined based on the treatment the patients were assigned. |
| Safety | All randomized patients who receive at least 1 dose of the randomly assigned IP.<br>Treatment group will be defined based on the treatment the patients were assigned. |

Abbreviation: IP = investigational product.

## 10.3. Statistical Analyses

### *10.3.1. General Statistical Considerations*

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of data will be conducted, as deemed appropriate.

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

Efficacy analyses will be conducted on all randomized patients according to the treatment the patients are assigned. The analyses for the primary and multiplicity-adjusted objectives will be performed for the efficacy estimand including data collected prior to permanent discontinuation of IP and for the ITT estimand including all data collected through Week 16 regardless of IP use (Section 10.3.3.1). Unless otherwise specified, the efficacy analyses for other secondary objectives and exploratory objectives will be performed for the efficacy estimand. When change from baseline is included as a response variable of analysis models, the patient will be included in the analysis only if a baseline and a postbaseline measurement are available.

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

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10. Countries in similar geographic regions with fewer than 10 patients, based on the all-randomized population, will be

pooled to achieve a pooled country of at least 10 patients. All analyses using country in the model will use a pooled country, unless otherwise specified. The final pooling by country and geographic region will be finalized prior to data lock.

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

Baseline is defined as the last nonmissing measurement at or before the randomization visit (Visit 4) unless otherwise specified.

A restricted-maximum-likelihood-based, mixed model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment, strata (pooled country and patient's personal CGM use during the study), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. For analyses of variables other than HbA1c, the HbA1c stratum (≤7.5%, >7.5%) will be included in the model. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on least-squares (LS) means and Type III tests. SAS PROC MIXED will be used to perform the analysis. If this analysis fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Compound symmetry with heterogeneous variances
- Toeplitz
- Autoregressive
- Compound symmetry without heterogeneous variances.

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

An analysis of covariance (ANCOVA) will also be used to analyze continuous variables collected only at baseline and endpoint. The model will include treatment and strata (pooled country, HbA1c stratum (≤7.5%, >7.5%), and patient's personal CGM use during the study) as fixed effects and baseline as a covariate. Unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward (LOCF) approach, using only postbaseline data.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-square 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.

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

## *10.3.2. Treatment Group Comparability*

### 10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided. Frequency counts and percentages of all patients entered, enrolled, randomized, completing, and/or discontinuing from the study will be presented for each treatment group. Reasons for discontinuation from study treatment and from the study during the treatment period will be summarized and compared between treatment groups using Fisher's exact tests. Reasons for discontinuation from the study during the lead-in and follow-up periods will be summarized.

### 10.3.2.2. Patient Characteristics

Standard baseline characteristics of age, sex, ethnicity, race, height, weight, and BMI will be summarized for all randomized patients. Summary statistics will include sample size, mean, SD, median, minimum, and maximum for continuous measures and sample size, frequency, and percent for categorical measures. Comparisons between treatment groups will be performed using Fisher's exact test or Pearson's chi-square test for categorical data and an analysis of variance (ANOVA) with treatment in the model for continuous data. Baseline diabetes characteristics (including pump brand/model) will be summarized in a similar manner.

Medical history and AEs at baseline will be summarized by preferred term (PT) within system organ class, and comparison between treatment groups will be performed using Fisher's exact test.

### 10.3.2.3. Concomitant Therapy

The type of rapid-acting insulin therapy, and the total, basal and bolus insulin doses at study entry and at baseline will be compared between treatment groups using Fisher's exact tests and ANOVA with treatment in the model.

Concomitant medications used during the treatment period will be summarized and compared between treatment groups using Fisher's exact test.

## *10.3.3. Efficacy Analyses*

### 10.3.3.1. Primary Analyses

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

For the US FDA submission, the primary analysis will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand (treatment regimen estimand) which will include all data collected regardless of IP use. The reference for each treatment group will be from the retrieved dropout patients who discontinue IP but have the measurement at the primary endpoint in the same treatment group. If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis, the reference will be changed to include all observed data from all randomized patients in the same treatment arm who complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog from the ANCOVA analysis of change from baseline to Week 16 in HbA1c using all randomized patients as described in Section 10.3.1.

For non-FDA submissions and publications, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog at Week 16 (Visit 13) from the MMRM analysis of change from baseline in HbA1c including data collected from all randomized patients prior to permanent discontinuation of IP through Week 16 (efficacy estimand). The analysis model and selection of covariance structure is described in Section 10.3.1.

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

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

#### *10.3.3.1.1. Sensitivity Analyses for Missing Data*

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

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

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

### 10.3.3.2. Secondary Analyses

A graphical approach for multiple comparisons will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the following multiplicity adjusted objectives: superiority of LY900014 compared with Humalog for 1-hour PPG during MMTT at Week 16, 2-hour PPG during MMTT at Week 16, change from baseline to Week 16 in HbA1c, the duration of time glucose values are within target range during a 24-hour period at Week 16, and the duration of time glucose values are within target range during daytime (0600 hours to midnight) at Week 16. The glucose target range is defined as 70 to 180 mg/dL (3.9 to 10.0 mmol/L), both inclusive, obtained from CGM.. Analyses will be performed for both the efficacy estimand and ITT estimand as described in Section 10.3.3.1 using the same graphical testing scheme.

The graphical testing scheme will be described in the SAP. The study total alpha level (or study-wise type I error) is preset to be 5% for each estimand. The study total alpha level will be used for the primary objective in the initial step. The alpha level will be allocated to other key endpoints based on the weights in testing paths once the primary endpoint is successfully demonstrated. If 1 of the remaining hypotheses is successfully demonstrated with the preserved alpha level, its preserved alpha will be allocated to the remainder of the hypotheses by the weights in the paths. The iterative test procedure continues until none of the remaining hypotheses can be demonstrated with their preserved alphas or all hypotheses are demonstrated successful.

An ANCOVA model as described in Section 10.3.1 will be used to analyze the 1-hour and 2-hour PPG. However, if the percentage of the patients with missing MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead. Analysis details will be documented in the SAP.

For continuous longitudinal secondary endpoints, the MMRM model similar to that for the primary analysis will be used with HbA1c stratum (≤7.5%, >7.5%) added as a fixed effect. Duration and percent time in range, time in hypoglycemia and time in hyperglycemia derived from CGM data will also be analyzed using MMRM model with HbA1c stratum (≤7.5%, >7.5%) as a fixed effect. Continuous nonlongitudinal secondary endpoints will be analyzed using the ANCOVA model with treatment and strata as fixed effects and baseline as a covariate. Treatment comparisons for the proportion of patients with HbA1c <7.0% and ≤6.5% will be analyzed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c by visit interaction, and treatment-by-visit interaction. Actual and change from baseline in basal, bolus, and total dose, as well as the bolus/total insulin dose ratio will be analyzed by the MMRM models described in Section 10.3.1.

### 10.3.3.3. Tertiary/Exploratory Analyses

Continuous variables and the change from baseline for these variables will be analyzed by either

MMRM or ANCOVA models described in Section 10.3.1. Categorical variables will be analyzed either by models (for example, logistic regression) or by Fisher's exact test or Pearson's chi-square test. Analysis details for the tertiary endpoints will be described in the SAP.

### *10.3.4. Safety Analyses*

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

Events that are newly reported after the first dose of IP or reported to worsen in severity from baseline will be considered TEAEs. 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.

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

Hypoglycemia rates will be summarized for periods of 1 year and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical method (details will be described in the SAP). For each of other categories of hypoglycemia, the number of hypoglycemia events during a specific period (rate) after randomization (for example, 0 to 4 weeks of treatment period) will be analyzed by using a negative binomial regression model including treatment. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days will be included in the model to estimate the rate of hypoglycemia per year. The proportion of patients with at least 1 hypoglycemic event in each category (incidence) during a specific period after randomization will be analyzed using a logistic regression model including treatment.

Similarly, a negative binomial model and a logistic regression model including treatment will be used to analyze the rate of pump occlusion alarms leading to unplanned infusion set changes per 30 days, and the proportion of patients with at least 1 occlusion alarm (incidence) leading to unplanned infusion set changes, respectively.

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

The analyses for assessing immunogenicity data will be described in the SAP after being agreed with the FDA on the threshold for determining treatment-emergent antibodies to insulin lispro.

## *10.3.5. Other Analyses*

### 10.3.5.1. Health Economics

Summary statistics, including number of patients and proportion of categorical outcomes (5 levels) for the 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) of the EQ-5D-5L will be provided by visit and by treatment. The change from baseline to LOCF endpoint (Week 16, Visit 13) in the EQ-5D-5L UK population-based health state index score and EQ-VAS score will be analyzed using the ANCOVA model described in the Section 10.3.1.

For the ITSQ, the change from baseline to LOCF endpoint while on treatment in each domain transformed score (inconvenience, lifestyle, hypoglycemic control, glycemic control, and delivery system) and overall transformed score will be analyzed using the ANCOVA model described the Section 10.3.1.

### 10.3.5.2. Subgroup Analyses

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

- Age (<40 years, ≥40 years)
- HbA1c stratum (≤7.5%, >7.5%)
- Patient's personal CGM use during the study (yes/no)
- Patient's use of low glucose suspends during the study (yes/no)
- Sex (Male or Female)
- BMI (<25, ≥25 $kg/m^2$ )
- Bolus delivery speed at study entry
- Duration of Diabetes (using the median as the cutoff)
- Race
- Ethnicity
- Country
- Region

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

Additional subgroup analyses may also be performed.

### *10.3.6. Interim Analyses*

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.

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# 12. Appendices

# Appendix 1. Abbreviations and Definitions

| Term | Definition |
|---|---|
| **1,5-AG** | 1,5-Anhydroglucitol |
| **AE** | adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. |
| **AIT** | active insulin time |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **ANCOVA** | analysis of covariance |
| **ANOVA** | analysis of variance |
| **AST** | aspartate aminotransferase |
| **BG** | blood glucose |
| **blinding/masking** | A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment, but the investigator and/his staff and the patient are not.<br>A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received. |
| **BMI** | body mass index |
| **CF** | correction factor |
| **CGM** | continuous glucose monitoring |
| **CI** | confidence interval |
| **CRF** | case report form |
| **Product complaint** | Product complaints are a customer's written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. |
| **CR** | Carbohydrate ratio |

| | |
|---|---|
| **CRP/CRS** | clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer. |
| **CSII** | continuous subcutaneous insulin infusion |
| **CSR** | clinical study report |
| **ECG** | electrocardiogram |
| **EDC** | electronic data-capture |
| **eCRF** | electronic case report form |
| **eGFR** | estimated glomerular filtration rate |
| **enroll** | The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment. |
| **enter** | Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives. |
| **EQ-5D-5L** | European Quality of Life – 5 Dimensions 5 Level |
| **ERB** | ethical review board |
| **FBG** | fasting blood glucose |
| **FDA** | Food and Drug Administration |
| **FGM** | flash glucose monitoring |
| **GCP** | good clinical practice |
| **GD** | glucodynamic(s) |
| **GRAS** | Generally Recognized As Safe |
| **HbA1c** | hemoglobin A1c |
| **HCP** | health care provider |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |

| | |
|---|---|
| **IM** | intramuscular |
| **IP** | investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. |
| **ISF** | Insulin sensitivity factor |
| **ITSQ** | Insulin Treatment Satisfaction Questionnaire |
| **ITT** | intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment. |
| **IV** | intravenous |
| **IWRS** | interactive web-response system |
| **LLT** | lowest level term |
| **LOCF** | last observation carried forward |
| **LS** | least squares |
| **MAR** | missing at random |
| **MDI** | multiple daily injections |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MMRM** | mixed-effect model repeated measure |
| **MMTT** | Mixed-meal tolerance test |
| **NIM** | noninferiority margin |
| **NPH** | neutral protamine Hagedorn |
| **PD** | Pharmacodynamic(s) |
| **PK** | pharmacokinetic(s) |
| **PPG** | postprandial glucose |
| **PT** | preferred term |

| | |
|---|---|
| **RBA** | radio ligand-binding assay |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **SC** | subcutaneous |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| **SD** | standard deviation |
| **SMBG** | self-monitored blood glucose |
| **SUSARs** | suspected unexpected serious adverse reactions |
| **T1D** | type 1 diabetes |
| **T2D** | type 2 diabetes |
| **TBL** | total bilirubin level |
| **TEAE** | treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment. |
| **ULN** | upper limit of normal |
| **Unexplained Hyperglycemia** | High blood glucose (≥300 mg/dL) that cannot be explained by a missed prior bolus, dietary indiscretion, rebound or treatment of hypoglycemia, a pump failure, an empty pump reservoir, an infusion set complication (e.g.; kinked, came out, leaking), or an infusion site complication (e.g.; pain, redness). |
| **VAS** | visual analog scale |

# Appendix 2. Clinical Laboratory Tests

**Clinical Laboratory Tests[a]**

| **Hematology** | **Clinical Chemistry(Serum Concentrations of):** |
|---|---|
| Hemoglobin | Sodium |
| Hematocrit | Potassium |
| Erythrocyte count (RBC) | Total bilirubin |
| Mean cell volume | Direct bilirubin |
| Mean cell hemoglobin concentration | Alkaline phosphatase |
| Leukocytes (WBC) | Alanine aminotransferase (ALT) |
| Neutrophils, segmented | Aspartate aminotransferase (AST) |
| Lymphocytes | Blood urea nitrogen (BUN) |
| Monocytes | Creatinine |
| Eosinophils | Uric acid |
| Basophils | Calcium |
| Platelets | Chloride |
| | Magnesium |
| **Urinalysis** | Total protein |
| Specific gravity | Glucose |
| pH | Albumin |
| Protein | Creatine kinase (CK) |
| Glucose | eGFR (calculated by MDRD equation)[b] |
| Ketones | |
| Blood | 1,5 Anhydroglucitol |
| Urine leukocyte esterase | HbA1c |
| Bilirubin | |
| Nitrite | |
| **Serology** | |
| Anti-insulin lispro antibodies | |
| Pregnancy test (females only)[c] | |
| Follicle-stimulating hormone[d] | |

Abbreviations: eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin A1c IP = investigational product; MDRD = Modification of Diet in Renal Disease Study; RBC = red blood cells; WBC = white blood cells.

[a] All laboratory tests will be assayed by a Lilly-designated central laboratory, unless otherwise noted.

[b] MDRD: $175 \times [SCr] - 1.154 \times [age] - 0.203 \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]$; SCr = serum creatinine (mg/dL), final value will be expressed as mL/min/1.73 $m^2$.

[c] Serum pregnancy test must be performed in women of childbearing potential at Visit 1 followed by a urine pregnancy test within 24 hours prior to IP exposure at randomization and at other times at the investigator's discretion. When required per local regulations and/or institutional guidelines, local pregnancy testing will occur at mandatory times during the study treatment period.

[d] Follicle-stimulating hormone test must be performed at Visit 1 for a postmenopausal woman who is between 50 and 54 years of age (inclusive) with an intact uterus, not on hormone therapy, and who has had at least 6 months of spontaneous amenorrhea.

# Appendix 3. Study Governance Considerations

# Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

## *Appendix 3.1.1. Informed Consent*

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product (IP).
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

## *Appendix 3.1.2. Ethical Review*

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the informed consent form (ICF) must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on good clinical practice (GCP).

The study site's ERB(s) should be provided with the following:

- the current Investigator's Brochure (IB) and updates during the course of the study
- ICF
- relevant curricula vitae.

## *Appendix 3.1.3. Regulatory Considerations*

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

### *Appendix 3.1.4. Investigator Information*

A physician with expertise treating patients with type 1 diabetes (T1D) and experience in clinical trials.

### *Appendix 3.1.5. Protocol Signatures*

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

### *Appendix 3.1.6. Final Report Signature*

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An investigator will be selected by the Lilly study team to serve as the CSR coordinating Investigator. The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

## Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

### *Appendix 3.2.1. Data Capture System*

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data-capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment data (questionnaires and self-reported diary data) will be collected by the subject, via a paper source document and will be transcribed by the investigator-site personnel into the EDC system.

Data collected via the sponsor-provided data capture system will be stored with a third party. The investigator will have continuous access to the data during the study and until decommissioning of the data-capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

## Appendix 3.3. Study and Site Closure

### *Appendix 3.3.1. Discontinuation of Study Sites*

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

### *Appendix 3.3.2. Discontinuation of the Study*

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

# Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

**Hepatic Monitoring Tests**

| | |
|---|---|
| **Hepatic Hematology[a]** | **Haptoglobin[a]** |
| Hemoglobin | |
| Hematocrit | **Hepatic Coagulation[a]** |
| RBC | Prothrombin Time |
| WBC | Prothrombin Time, INR |
| Neutrophils, segmented | |
| Lymphocytes | **Hepatic Serologies[a,b]** |
| Monocytes | Hepatitis A antibody, total |
| Eosinophils | Hepatitis A antibody, IgM |
| Basophils | Hepatitis B surface antigen |
| Platelets | Hepatitis B surface antibody |
| | Hepatitis B Core antibody |
| **Hepatic Chemistry[a]** | Hepatitis C antibody |
| Total bilirubin | Hepatitis E antibody, IgG |
| Direct bilirubin | Hepatitis E antibody, IgM |
| Alkaline phosphatase | |
| ALT | **Anti-nuclear antibody[a]** |
| AST | |
| GGT | **Alkaline Phosphatase Isoenzymes[a]** |
| CPK | |
| | **Anti-smooth muscle antibody (or anti-actin antibody)[a]** |

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory (if test results are required urgently to manage patient care).

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

# Appendix 5. Classification of Contraceptive Methods

Women of childbearing potential must use either 1 highly effective method of contraception or a combination of 2 effective methods of contraception. The patient may choose to use a double-barrier method of contraception (see chart below).

- Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

### Methods of Contraception

| Highly Effective Methods of Contraception | Effective Methods of Contraception (Must Use Combination of 2 Methods) |
|---|---|
| • Combined oral contraceptive pill and mini-pill<br>• NuvaRing®<br>• Implantable contraceptives<br>• Injectable contraceptives (such as Depo-Provera®)<br>• Intrauterine device (such as Mirena® and ParaGard®)<br>• Contraceptive patch – ONLY women <198 lb or 90 kg<br>• Bilateral tubal occlusion<br>• Total abstinence[a]<br>• Vasectomy | • Male condom with spermicide<br>• Female condom with spermicide<br>• Diaphragm with spermicide<br>• Cervical sponge with spermicide<br>• Cervical cap with spermicide |

[a] Total abstinence (as patient's preferred and usual lifestyle) or in a same-sex relationship (as part of patient's preferred and usual lifestyle). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

# Appendix 6. Protocol Amendment I8B-MC-ITRO (c) Summary
# A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog in Adults with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion PRONTO-Pump-2

## Overview

Protocol **I8B-MC-ITRO A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog in Adults with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion PRONTO-Pump-2** has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

**Amendment Summary for Protocol I8B-MC-ITRO Amendment (c)**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Section 1, Synopsis**<br>**Section 4, Objectives and Endpoints** | The secondary objectives of 1- and 2-hour postprandial glucose excursions were changed to 1- and 2-hour postprandial glucose.<br><br>The secondary objective that compared glucose time in range (70-180 mg/dL) during the 24-hour period for LY900014 and Humalog is now controlled for Type I error and included with the multiplicity adjusted objectives.<br><br>The glucose time in range (70-180 mg/dL) during the daytime period (6 am to midnight) for LY900014 and Humalog was added and is controlled for Type I error and included with the multiplicity adjusted objectives. | PPG excursion endpoints were changed to actual PPG measurements based on improvements in both fasting and postprandial glucose observed in Study I8B-MC-ITSI and predicted in PK/PD models with administration of LY900014 by CSII. The use of absolute 1- and 2-hour PPG values, rather than PPG excursions, will provide a more complete evaluation of the glycemic benefit offered by LY900014 during CSII, and it is expected that this change will result in greater power to detect differences between treatment groups in this study. |
| **Section 9.1.2, Secondary Efficacy Assessments** | 'Excursions' and 'minus fastings serum glucose' were removed from the secondary efficacy measure of 'Fasting and PPG collected during the MMTT' to reflect the change in objectives. | |
| **Section 10.3.3.2, Secondary Analyses** | 'Excursion' was removed from the 1 and 2-hour PPG secondary objective to reflect the change in objectives. | |

| | | |
|---|---|---|
| | Also, the duration of time glucose values was within the target range of 70 and 180 mg/dL during the daytime (6 am to midnight) and 24-hour period was added the secondary analyses. | Time in range endpoints were added as this measure is becoming of increasing importance to patients and prescribers, as evidenced in recent consensus statements from ADA (Battelino et al., 2019). All patients in the study will undergo several blinded CGM evaluation periods; these data will form the basis for the TIR analyses. Measurements were added to evaluate time in range over a 24-hour time period and also over the daytime period (6 am to midnight). Including these measures in the graphical approach allows us to control the type I error and correct for multiplicity, meaning that these endpoints, if positive, may be suitable for inclusion in product labeling. |

# Revised Protocol Sections

| | |
|---|---|
| **Note:** | Deletions have been identified by ~~strikethroughs~~.<br>Additions have been identified by the use of underscore. |

## Section 1 Synopsis and Section 4 Objectives and Endpoints

**Objective(s)/Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | |
| 1. To test the hypothesis that LY900014 is noninferior to Humalog on glycemic control ([NIM = 0.4% for HbA1c) in patients with T1D using CSII for 16 weeks | 1. Difference between LY900014 and Humalog in change from baseline to Week 16 in HbA1c |
| **Multiplicity Adjusted Objectives** | |
| 2. To test the hypothesis that LY900014 is superior to Humalog in controlling 1-hour postprandial glucose (PPG) ~~excursions~~ | 2. Difference between LY900014 and Humalog ~~in change from baseline to Week 16~~ in the 1-hour PPG ~~excursion~~ (serum glucose measured 1 hour after the start of the meal ~~minus fasting serum glucose~~) from a MMTT at Week 16 ~~and change from baseline to Week 16~~ |
| 3. To test the hypothesis that LY900014 is superior to Humalog in controlling 2-hour PPG ~~excursions~~ | 3. Difference between LY900014 and Humalog ~~in change from baseline to Week 16~~ in the 2-hour PPG ~~excursion~~ (serum glucose measured 2 hours after the start of the meal ~~minus fasting serum glucose~~) from a MMTT at Week 16 ~~and change from baseline to Week 16~~ |
| 4. To test the hypothesis that LY900014 is superior to Humalog on improving glycemic control (HbA1c) | 4. Difference between LY900014 and Humalog in change from baseline to Week 16 in HbA1c |
| 5. To test the hypothesis that LY900014 is superior to Humalog in the duration of time glucose values within target range 70 to 180 mg/dL (3.9 to 10.0 mmol/L), obtained from CGM use during 24-hour period | 5. Duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period, from each 14-day CGM session at Week 16 |
| 6. To test the hypothesis that LY900014 is superior to Humalog in the duration of time glucose values within target range 70 to 180 mg/dL (3.9 to10.0 mmol/L), obtained from CGM use during daytime | 6. Duration (in minutes and percentage of time) with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to daytime (0600 hours to midnight), from each 14-day CGM session at Week 16 |
| **Other Secondary Objectives** | |
| 7. To compare LY900014 and Humalog with respect to the rate of severe hypoglycemic events | 7. Rate (events/ patient/100 years) of severe hypoglycemic events from baseline through Week 16 |

| | |
|---|---|
| 8. To compare LY900014 and Humalog with respect to the rate and incidence of documented postmeal hypoglycemia | 8. Rate (events/patient/year) and incidence (percent of patients with at least 1 event) of documented postmeal hypoglycemia within 1 and 2 hours after the start of the meal from baseline through Week 16 |
| 9. To compare LY900014 and Humalog with respect to the rate and incidence of documented hypoglycemia | 9. Rate (events/patient/year) and incidence (percentage of patients with events) of documented hypoglycemic events from baseline through Week 16 |
| 10. To compare LY900014 and Humalog with respect to 1,5-AG | 10. Change from baseline 1,5-AG values at Week 16 |
| 11. To compare LY900014 and Humalog with respect to 10-point SMBG profiles | 11. Change from baseline 10-point SMBG values at Week 16 |
| 12. To compare LY900014 and Humalog with respect to total, basal, and bolus insulin dose | 12. Change from baseline in bolus/total insulin dose ratio at Week 16 |
| 13. To compare LY900014 and Humalog with respect to the proportion of patients achieving HbA1c targets | 13. The proportion of patients with HbA1c <7% and ≤6.5% at Week 16 |
| ~~To compare LY900014 and Humalog with respect to the duration of time glucose values are within target range (70 and 180 mg/dL [3.9 and 10.0 mmol/L]), obtained from CGM use~~ | ~~Duration (in minutes) and percentage of time with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period, from each 14-day CGM session at Week 16~~ |
| 14. To compare LY900014 and Humalog with respect to the duration of time spent in hypoglycemic glucose ranges, obtained from CGM use | 14. Duration (in minutes) and percentage of time with glucose values <54 and <70 mg/dL (3.0 and 3.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes <54 and <70 mg/dL, from each 14-day CGM session at Week 16 |
| 15. To compare LY900014 and Humalog with respect to the duration of time spent in hyperglycemic glucose ranges, obtained from CGM use | 15. Duration (in minutes) and percentage of time with glucose values >180 and >250 mg/dL (10.0 and 13.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes >180 and >250 mg/dL, from each 14-day CGM session at Week 16 |
| 16. To compare LY900014 and Humalog with respect to the incidence and rate of pump occlusion alarms that lead to an unplanned infusion set change | 16. Rate (events/patient/30 days) and incidence (percent of patients with at least 1 event) of pump occlusion alarms that lead to an unplanned infusion set change from baseline through Week 16 |
| 17. To compare LY900014 and Humalog with respect to the incidence and rate of episodes of unexplained hyperglycemia that lead to an unplanned infusion set change | 17. Rate (events/patient/30 days) and incidence (percent of patients with at least 1 event of unexplained hyperglycemia > 300 mg/dL confirmed by SMBG that leads to an unplanned infusion set change from baseline through Week 16 |

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

### Section 9.1.2 Secondary Efficacy Assessments

- Fasting and PPG collected during the MMTT:
    - 1-hour and 2-hour PPG ~~excursions~~: serum glucose measured 1 hour and 2 hours after the start of the meal ~~minus fasting serum glucose~~
    - Incremental areas under the serum glucose concentration-time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after a meal; maximum serum glucose after a meal
    - Glucose variability measured by the coefficient of variation and standard deviation (SD)
- 1,5-Anhydroglucitol (1,5-AG)
- SMBG 10-point profiles:
    - 1-hour and 2-hour PPG and PPG excursions by meal and across all meals
    - Within- and between-day glucose variability measured by the coefficient of variation and SD
- CGM
    - Duration and percentage of time in range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime (0600 hours to midnight) and 24-hour period obtained by study-provided Dexcom blinded CGM
    - Duration and percentage of time with glucose values <54 and <70 mg/dL (3.0 and 3.9 mmol/L)

### Section 10.3.3.2 Secondary Analyses

## Secondary Analyses

A graphical approach for multiple comparisons will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the following multiplicity adjusted objectives: superiority of LY900014 compared with Humalog for 1-hour PPG ~~excursion~~ during MMTT at Week 16, 2-hour PPG ~~excursion~~ during MMTT at Week 16, ~~and~~ change from baseline to Week 16 in HbA1c, the duration of time glucose values are within target range during daytime (0600 hours to midnight) at Week 16. The glucose target range is desfined as 70 to 180 mg/dL (3.9 to 10.0 mmol/L), both inclusive, obtained from CGM .

Analyses will be performed for both the efficacy estimand and ITT estimand as described in Section 10.3.3.1 using the same graphical testing scheme.

The graphical testing scheme will be described in the SAP. The study total alpha level (or study-wise type I error) is preset to be 5% for each estimand. The study total alpha level will be used for the primary objective in the initial step. The alpha level will be allocated to other key endpoints based on the weights in testing paths once the primary endpoint is successfully demonstrated. If 1 of the remaining hypotheses is successfully demonstrated with the preserved alpha level, its preserved alpha will be allocated to the remainder of the hypotheses by the weights in the paths. The iterative test procedure continues until none of the remaining hypotheses can be demonstrated with their preserved alphas or all hypotheses are demonstrated successful.

An ANCOVA model as described in Section 10.3.1 will be used to analyze the 1-hour and 2-hour PPG ~~excursions~~. However, if the percentage of the patients with missing MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead. Analysis details will be documented in the SAP.

For continuous longitudinal secondary endpoints, the MMRM model similar to that for the primary analysis will be used with HbA1c stratum (≤7.5%, >7.5%) added as a fixed effect. Duration and percent time in range, time in hypoglycemia and time in hyperglycemia derived from CGM data will also be analyzed using MMRM model with HbA1c stratum (≤7.5%, >7.5%) as a fixed effect. Continuous nonlongitudinal secondary endpoints will be analyzed using the ANCOVA model with treatment and strata as fixed effects and baseline as a covariate. Treatment comparisons for the proportion of patients with HbA1c <7.0% and ≤6.5% will be analyzed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c by visit interaction, and treatment-by-visit interaction. Actual and change from baseline in basal, bolus, and total dose, as well as the bolus/total insulin dose ratio will be analyzed by the MMRM models described in Section 10.3.1.

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