

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

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LY900014

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Protocol Electronically Signed and Approved by Lilly: 23 October 2017  
Amendment (a) Electronically Signed and Approved by Lilly  
on approval date provided below.

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## 1. Synopsis

### Title of Study:

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

### Rationale:

Insulin pumps use only rapid-acting insulin for both basal and bolus insulin requirements. Basal insulin is a continuous infusion of insulin that is delivered automatically 24 hours a day. The purpose of basal insulin is to cover hepatic glucose production and maintain glucose stability during fasting states (between meals and during sleep). Bolus insulin is delivered “on-demand,” by the patient, for food intake and/or to correct glucose levels that are above the patient’s target range, delivered separately or together.

Because insulin pump therapy uses only rapid-acting insulin, the onset of diabetic ketoacidosis (DKA) can occur quickly if insulin delivery is interrupted for a period of time. The most important DKA prevention strategies are: 1) adhering to a routine blood glucose (BG) monitoring/continuous glucose monitoring schedule and 2) never ignoring an unexplained high BG. A high BG level that is not responding to a correction bolus via insulin pump may indicate an infusion set occlusion or insulin pump malfunction.

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

### Objective(s)/Endpoints:

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

Objectives	Endpoints
<b>Secondary Objectives</b>	
2. To compare LY900014 and insulin lispro with respect to the incidence of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump	2. Incidence (percent of patients with at least 1 event) of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump, during the 6-week treatment period
3. To compare LY900014 and insulin lispro with respect to the rate and incidence of premature infusion set changes	3. Rate (events/patient/30 days) and incidence of premature infusion set changes by reason (infusion set kinked, came out, or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other) during the 6-week treatment period
4. To compare LY900014 and insulin lispro with respect to the time interval until infusion set change	4. Time interval until infusion set change during the 6-week treatment period
5. To compare LY900014 and insulin lispro with respect to total, basal, and bolus insulin dose	5. Bolus/total insulin dose ratio at the end of the 6-week treatment period
6. To compare LY900014 and insulin lispro with respect to the interstitial glucose reduction rate from hyperglycemia following a non-meal-related correction bolus delivered via the pump	6. Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >180 mg/dL [10 mmol/L]) to recovery (interstitial glucose ≤180 mg/dL), from up to 6 weeks of CGM use
7. To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	7. Rate (events/patient/100 years) of severe hypoglycemic events during the 6-week treatment period

Abbreviations: CGM = continuous glucose monitoring; SMBG = self-monitored blood glucose.

**Summary of Study Design:**

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

**Treatment Arms and Duration:**

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

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

Sequence A: LY900014 → insulin lispro

Sequence B: insulin lispro → LY900014

**Number of Participants:**

Approximately 60 participants will be screened to achieve 48 randomized patients and approximately 42 patients completing 12 weeks of treatment.

**Statistical Analysis:**

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

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

Baseline is defined as the last non-missing measurement at or before the randomization visit (Visit 3), unless otherwise specified.

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

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

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

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

The analyses of the primary objective will be conducted on the Safety Population including data collected prior to permanent discontinuation of investigational product (ie, last dose) in each randomized treatment period (Period I and Period II) and excluding data (if any) that are collected while patients temporarily are off pump or off IP. Treatment group comparisons will be performed using Wilcoxon signed-rank test at the full significance level of 0.05, with patients who are dosed in both treatment periods. No multiplicity adjustments will be made for the analysis of secondary and exploratory objectives.

The incidence (percent of patients with at least 1 event) of infusion set failure as defined in the primary objective, premature infusion set changes by reason, and severe hypoglycemia will be analyzed using Prescott's exact test.

The Wilcoxon signed-rank test will be used to analyze the rate of premature infusion set changes by reason, and severe hypoglycemia, as described above for the primary endpoint.

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

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

## 2. Schedule of Activities

Table ITSI.1. Schedule of Activities

Study Procedure	Study Screening	Lead-in Period	Study Period I				Study Period II			Safety Follow-up	ED
			3	4	5 <sup>a</sup>	6	7	8 <sup>a</sup>	9		
eCRF Visit Number	1	2	3	4	5 <sup>a</sup>	6	7	8 <sup>a</sup>	9	801	ED
Visit Window (± days)	0	3	3	3	3	3	3	3	3	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-3	-2	0	2	4	6	8	10	12	16	
Informed consent signed	X										
IWRS	X	X	X	X	X	X	X	X	X	X	X
Patient eligibility review	X										
Randomization <sup>b</sup>			X								
<b>Clinical Assessments</b>											
Patient demographics	X										
Medical history and preexisting conditions	X										
Physical exam/height	X										
Record pump model and reservoir size <sup>c</sup>	X										
Set pump bolus delivery speed to Standard (1.5 U/minute)		X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse events and product complaints <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X
Train patient on use of eCOA to enter all infusion set and reservoir changes and all non-meal-related correction boluses <sup>e</sup>		X									
Review/remind subjects of entering non-meal-related correction boluses			X	X	X	X	X	X	X		X
Review infusion set and reservoir changes, pump occlusion alarms, and suspected occlusions from eCOA <sup>f</sup>		X	X	X	X	X	X	X	X		X
Remind patient to monitor SMBG following all non-meal-related correction boluses for unexplained hyperglycemia <sup>e</sup>		X	X	X	X	X	X	X			
Body weight <sup>g</sup>	X	X	X	X		X	X		X	X	X
Vital signs: blood pressure/pulse rate <sup>h</sup>	X	X	X	X		X	X		X	X	X

Study Procedure	Study Screening	Lead-in Period	Study Period I				Study Period II			Safety Follow-up	ED
			3	4	5 <sup>a</sup>	6	7	8 <sup>a</sup>	9		
eCRF Visit Number	1	2	3	4	5 <sup>a</sup>	6	7	8 <sup>a</sup>	9	801	ED
Visit Window (± days)	0	3	3	3	3	3	3	3	3	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-3	-2	0	2	4	6	8	10	12	16	
ECG (12-lead) <sup>i</sup>	X										
Educate patient on adjusting pump basal rates and bolus calculator settings <sup>j</sup>		X	X	X		X	X		X		
Transfer to insulin lispro <sup>k</sup>		X									
Crossover to alternate IP and reset pump to basal rates and bolus calculator settings used at randomization						X					
Start non-study rapid-acting analog and reset pump to basal rates and bolus calculator settings used at randomization									X		X
Change infusion set and reservoir at investigative site <sup>l</sup>		X	X			X			X <sup>m</sup>		X <sup>m</sup>
Optimize basal rates and bolus calculator settings <sup>n</sup>		X	X	X		X	X		X		
<b>Ancillary Supplies/Diaries/IP</b>											
Dispense pump infusion sets and reservoirs		X	X	X		X	X		X		
Dispense eCOA, glucometer, ancillary supplies, pair glucometer with eDiary and complete training		X									
Dispense ancillary supplies as needed		X	X	X		X	X		X		
Review unexplained hyperglycemia troubleshooting		X									
Dispense blood ketone meter and strips and train patient on use.		X									
Dispense IP <sup>o</sup>		X	X	X		X	X				
Train on collecting 4-point SMBG profiles <sup>p</sup>		X									
Review 4-point SMBG profiles <sup>q</sup>			X	X	X	X	X	X	X	X	X

Study Procedure	Study Screening	Lead-in Period	Study Period I				Study Period II			Safety Follow-up	ED
			3	4	5a	6	7	8a	9		
eCRF Visit Number	1	2	3	4	5a	6	7	8a	9	801	ED
Visit Window (± days)	0	3	3	3	3	3	3	3	3	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-3	-2	0	2	4	6	8	10	12	16	
Review pump data for use in clinical decision making and data entry of required fields into Inform <sup>f</sup>		X	X	X		X	X		X		
Record in Inform total basal and total bolus units for last 3 days prior to visit		X	X	X		X	X		X	X	X
Record in Inform total number of meal-related bolus doses given as Normal, Square Wave, and Dual Wave during the 7 days prior to visit		X	X	X		X	X		X	X	X
Record in Inform pump basal rates, CRs, ISFs, and AIT from last day prior to visit		X	X			X			X		X
Record in Inform the breakfast CR and ISF, and the AIT from last day prior to visit		X	X	X		X	X		X		X
Record in Inform any blood ketone meter test results			X	X		X	X		X		X
Review/discuss blood ketone meter test results, if applicable			X	X		X	X		X		X
Review/discuss hypoglycemia data			X	X	X	X	X	X	X	X	X
Train patient on CGM including use of event markers to record all breakfast meal times (carb event) and corresponding meal bolus times (insulin event) <sup>p</sup>		X									
Review CGM use of event markers and corresponding meal times			X	X	X	X	X	X	X		X
Pair CGM transmitter and receiver		X									
Dispense CGM sensors		X	X	X		X	X				
Insert new CGM sensor and attach transmitter at site during visit.		X	X			X					
Synchronize the times of pump, eCOA,		X	X	X		X	X				

Study Procedure	Study Screening	Lead-in Period	Study Period I				Study Period II			Safety Follow-up	ED
			3	4	5 <sup>a</sup>	6	7	8 <sup>a</sup>	9		
eCRF Visit Number	1	2	3	4	5 <sup>a</sup>	6	7	8 <sup>a</sup>	9	801	ED
Visit Window (± days)	0	3	3	3	3	3	3	3	3	7	
Time on Study Relative to First Active Treatment Dose (weeks)	-3	-2	0	2	4	6	8	10	12	16	
glucometer, ketone meter, and CGM receiver at site during visit											
Download and review CGM data for clinical decision making and transmit to secure cloud storage			X	X		X	X		X		X
Remind patient to change CGM sensor every 7 days		X	X	X	X	X	X	X			
Remove last CGM sensor, detach transmitter, and return transmitter and receiver to site									X		X
Drug accountability			X	X		X	X		X		X
Return eCOA devices										X	X
Patient returns used and unused study drug supplies (used and unused vials)			X	X		X	X		X		X
<b>Laboratory Assessments</b>											
Urinalysis panel	X										
Pregnancy test <sup>s</sup>	X		X								
Follicle-stimulating hormone test <sup>t</sup>	X										
Chemistry panel	X		X								
Hematology	X		X								
1.5-Anhydroglucitol			X			X			X		X
Hemoglobin A1c	X		X			X			X	X	X
Anti-insulin lispro antibodies		X	X			X			X	X	X

Abbreviations: AIT = active insulin time; CGM = continuous glucose monitoring; BG = blood glucose; CR = carb ratio; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment, eCRF = electronic case report form; ED = early discontinuation; IP = investigational product; ISF = insulin sensitivity factor; IWRS = interactive web response system; SMBG = self-monitored blood glucose.

<sup>a</sup> Telephone visits are indicated by shaded columns. Activities include: record visit in the IWRS; collect adverse events and concomitant medications; review of pump occlusion alarms and suspected occlusions; review BG readings and study drug doses; adjust CRs, ISFs, AIT and basal rates as needed; review hypoglycemic events; provide reminders regarding scheduled visits and SMBG profiles, as applicable.

- b Randomization should occur after completion of all Visit 3 procedures.
- c The MiniMed Mio infusion set with 6-mm length cannula and 23" tubing length will be provided for all patients to use during the study.
- d 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.
- e Non-meal-related correction boluses are not associated with a meal or combined with a meal bolus.
- f Infusion set and reservoir changes must be at same time.
- g Patients should be advised to remove their shoes/coats and empty their pockets before the body weight is obtained.
- h Vital sign 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.
- i Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- j Initial training at Visit 2 will include diabetes education, insulin pump education, and nutrition counseling. Training will include a review of correct pump use (frequency of reservoir and infusion set changes, infusion site rotation, carb counting, and adjusting pump basal rates and bolus calculator settings) and review patient's ability to trouble shoot unexplained hyperglycemia and treat hypoglycemia. Appropriate site personnel will administer training and education using locally approved diabetes education/training materials and programs or by using other materials that may be provided by the sponsor. Patients may be provided abbreviated training and education at visits following Visit 2 based upon patient needs.
- k Only for patients using insulin aspart or insulin glulisine.
- l Complete all study procedures prior to reservoir and infusion set change at Visits 2, 3, 6, and 9. Under the observation of site staff, patients will fill a new pump reservoir and infusion set, insert the infusion set cannula into an appropriate pump site, and begin infusion.
- m At Visit 9 or ED, start non-study rapid-acting insulin.
- n Investigators, in discussion with patients, adjust basal rates and CRs, ISFs, and AIT for calculating bolus and correction doses to meet the target BG levels.
- o Complete all study procedures prior to initiating IP at Visits 2, 3, and 6.
- p Training may be repeated at other visits, as needed.
- q Patients should be instructed to perform a minimum of 4-point SMBG profiles daily starting at Visit 2.
- r Enter into Inform current pump basal rates, CRs, ISFs, and AIT from Device Settings Snapshot; total basal units and total bolus units for last 3 days prior to visit, and total number of Normal, Square Wave, and Dual Wave bolus doses given during the last 7 days prior to the visit from Daily Detail report.
- s 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 (Visit 3) 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.
- t 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.

## 3. Introduction

### 3.1. Study Rationale

Prandial insulin with faster onset and/or faster offset characteristics might reduce glycemic excursions, time to recovery from hyperglycemia, and the incidence of delayed postprandial hypoglycemia compared to currently available rapid-acting insulin analogs. Rapid-acting insulins, such as Humalog<sup>®</sup>, have been shown to have a more rapid onset of action compared to human insulin; however, the general consensus is that they are not rapid enough to match carbohydrate absorption, whether delivered by pump or syringe/pen injector, limiting efficacy. An ultra-rapid-acting prandial insulin that would shift the pharmacokinetic and pharmacodynamic profiles of insulin to provide an even faster onset of action would better match carbohydrate absorption and allow for efficacious dosing immediately prior to meals. 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 (T1DM) and type 2 diabetes mellitus (T2DM) when delivered by multiple daily injections (MDI), continuous subcutaneous insulin infusion (CSII), or in the development of closed loop insulin delivery systems.

Insulin pumps use only rapid-acting insulin for both basal and bolus insulin requirements. Basal insulin is a continuous infusion of insulin that is delivered automatically 24 hours a day. The purpose of basal insulin is to cover hepatic glucose production and maintain glucose stability during fasting states (between meals and during sleep). Bolus insulin is delivered “on-demand,” by the patient, for food intake and/or to correct glucose levels that are above the patient’s target range, delivered separately or together.

Because insulin pump therapy uses only rapid-acting insulin, the onset of diabetic ketoacidosis (DKA) can occur quickly if insulin delivery is interrupted for a period of time. DKA develops when insulin levels are insufficient to meet the body’s basic metabolic requirements. DKA 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. The most important DKA prevention strategies are: 1) adhering to a routine blood glucose (BG) monitoring/continuous glucose monitoring (CGM) schedule and 2) never ignoring an unexplained high BG. A high BG that is not responding to a correction bolus via insulin pump may indicate an infusion set occlusion or insulin pump malfunction.

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

### 3.2. Background

There have been many advances in the treatment of T1DM in the last 20 years; however, reaching and maintaining glycemic goals remains challenging even under intensive insulin therapy regimens. Only approximately 30% of insulin-requiring patients with diabetes are able to reach the goal hemoglobin A1c (HbA1c) target of <7% (Stark Casagrande et al. 2013). Currently available rapid-acting insulin analogs continue to be unable to match the kinetics of physiological post-meal insulin secretion, which is biphasic. Thus, there remains a need to continue to develop formulations with a time-action profile that more closely approximates that of endogenous insulin secretion.

Ideally, currently available rapid-acting insulin analogs should be injected or bolused 10 to 15 minutes prior to meal consumption to control postprandial glucose (PPG). However, many people inject or bolus their rapid-acting insulin at the time of the meal or after the meal. According to survey data from the T1D Exchange on the timing of prandial insulin injection, 16.3% of patients indicated they inject 15 minutes prior to meals, 33% inject 1 to 14 minutes prior to meals, 38.6% inject at the time of the meal, and 12.1% inject after meals. Because patients often inject or bolus later than recommended, there is a greater mismatch between insulin action and postprandial BG elevations.

LY900014 is a formulation of insulin lispro developed as an ultra-rapid acting insulin with a faster onset of action and shorter duration of action compared to currently available rapid-acting insulin analogs. LY900014 contains the prostacyclin analog (treprostinil), citrate, and other excipients. This formulation involves the novel use of a microdose of treprostinil as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient that elicits a systemic effect. Treprostinil is a prostacyclin analog for the treatment of symptomatic pulmonary arterial hypertension, and has been approved in the United States since 2002 (Remodulin package insert, 2014) and in Europe since 2005 (PMR [WWW]). Sodium citrate, an excipient that speeds insulin absorption, is also included in the formulation to further enhance the absorption of insulin lispro. Sodium citrate and the other excipients in the LY900014 formulation are listed in the Food and Drug Administration (FDA) Generally Recognized As Safe food additives database and in the FDA Inactive Ingredients in Approved Drugs database. Furthermore, the excipient concentration in LY900014 is within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

Nine LY900014 Phase 1 clinical studies have been conducted to date in healthy subjects or patients with T1DM or T2DM. Across these studies, LY900014 has consistently demonstrated a faster time-action profile than Humalog. In patients with T1DM or T2DM treated with MDI insulin therapy, LY900014 significantly reduced PPG excursions compared to Humalog when both were dosed by syringe at the start of a test meal. Two studies in patients with T1DM have been completed using CSII in an in-patient setting, both of which have demonstrated accelerated time action. 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 package insert, 2014). All samples of treprostinil from LY900014 administration were below the lower limit of quantitation. The Investigator's Brochure (IB) describes the clinical and nonclinical development of LY900014.

### **3.3. Benefit/Risk Assessment**

In Phase 1 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 insulin lispro.

More detailed information about the known and expected benefits and risks of insulin lispro may be found in the country-specific product labeling (for example, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics).

Safety evaluation in this study will include hypoglycemia, treatment-emergent adverse event (TEAEs), serious adverse events (SAEs), clinical laboratory assessments, anti-insulin lispro antibodies, CGM, frequent visits, ketone testing, 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 ITSI.2 shows the objectives and endpoints of the study.

**Table ITSI.2. Objectives and Endpoints**

Objectives	Endpoints
<b>Primary Objective</b>	
1. To compare LY900014 and insulin lispro with respect to the rate of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump	1. Rate (events/patient/30 days) of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump, during the 6-week treatment period
<b>Secondary Objectives</b>	
2. To compare LY900014 and insulin lispro with respect to the incidence of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump	2. Incidence (percent of patients with at least 1 event) of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump, during the 6-week treatment period
3. To compare LY900014 and insulin lispro with respect to the rate and incidence of premature infusion set changes	3. Rate (events/patient/30 days) and incidence of premature infusion set changes by reason (infusion set kinked, came out, or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other) during the 6-week treatment period
4. To compare LY900014 and insulin lispro with respect to the time interval until infusion set change	4. Time interval until infusion set change during the 6-week treatment period
5. To compare LY900014 and insulin lispro with respect to total, basal, and bolus insulin dose	5. Bolus/total insulin dose ratio at the end of the 6-week treatment period
6. To compare LY900014 and insulin lispro with respect to the interstitial glucose reduction rate from hyperglycemia following a non-meal-related correction bolus delivered via the pump	6. Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >180 mg/dL (10.0 mmol/L) to recovery (interstitial glucose ≤180 mg/dL), from up to 6 weeks of CGM use
7. To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	7. Rate (events/patient/100 years) of severe hypoglycemic events during the 6-week treatment period

Objectives	Endpoints
<b>Tertiary/Exploratory Objectives</b>	
8. To compare the safety of LY900014 and insulin lispro	8. Adverse events and vital signs
9. To compare LY900014 and insulin lispro with respect to the rate and incidence of documented symptomatic post-meal hypoglycemia	9. Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic post-meal hypoglycemia within 1 and 2 hours after the start of a meal during the last 2 weeks of the 6-week treatment period
10. To compare LY900014 and insulin lispro with respect to the rate and incidence of documented symptomatic hypoglycemia	10. Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with events) of documented symptomatic hypoglycemic events during the last 2 weeks of the 6-week treatment period
11. To compare LY900014 and insulin lispro with respect to the incremental AUCs after breakfast, obtained from CGM use	11. Incremental AUC <sub>0-1 hour</sub> after breakfast during the last 2 weeks of up to 6 weeks of CGM use
12. To compare LY900014 and insulin lispro with respect to the duration of time glucose values are within target range (71 and 180 mg/dL [3.9 and 10.0 mmol/L]), obtained from CGM use	12. Duration (in minutes) and percentage of time with glucose values between 71 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period, during the last 2 weeks of up to 6 weeks of CGM use
13. To compare LY900014 and insulin lispro with respect to the duration of time glucose values are within target range (71 and 140 mg/dL [3.9 and 7.8 mmol/L]), obtained from CGM use	13. Duration (in minutes) and percentage of time with glucose values between 71 and 140 mg/dL (3.9 and 7.8 mmol/L), both inclusive, normalized to a 24-hour period, during the last 2 weeks of up to 6 weeks of CGM use
14. To compare LY900014 and insulin lispro with respect to the glucose profiles, obtained from CGM use	14. Average glucose for a 24-hour period during the last 2 weeks of up to 6 weeks of CGM use
15. To compare LY900014 and insulin lispro with respect to the glucose variability, obtained from CGM use	15. Interquartile range, CV, LBGI, and HBGI during the last 2 weeks of up to 6 weeks of CGM use
16. To compare LY900014 and insulin lispro with respect to the factors affecting dosing in pumps	16. Actual and change from baseline in factors affecting dosing in pump (breakfast CR, AIT, breakfast ISF, and frequency of use of non-normal bolus type [Square Wave or Dual Wave]), during the 6-week treatment period
17. To compare LY900014 and insulin lispro with respect to the duration of time spent in hypoglycemic glucose ranges, obtained from CGM use	17. Duration (in minutes) and percentage of time with glucose values <50, <60, and ≤70 mg/dL (0.8, 3.3, and 3.9 mmol/L), normalized to a 24-hour period and number of episodes, defined as at least 10 consecutive minutes <50, <60, and ≤70 mg/dL, during the last 2 weeks of up to 6 weeks of CGM use

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

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

## 5. Study Design

### 5.1. Overall Design

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

The study is designed to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of infusion set failures that lead to premature infusion set changes due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump. The study includes a 1-week screening period and a 2-week lead-in period followed by a 2-period crossover and a 4-week post-treatment safety follow-up. Each period of the crossover will consist of 6 weeks of treatment with no washout between periods.

Unexplained hyperglycemia is expected to be an uncommon event in this study and the use of real-time CGM, self-monitored blood glucose (SMBG), electronic clinical outcomes assessment (eCOA), frequent study visits, and provision of standard of care hyperglycemia management guidelines and blood ketone testing meters and strips will all serve to maximize subject safety. Patients will be experienced pump users who have recent experience using CGM or flash glucose monitoring (FGM), and they will be guided to follow best standards of care in insulin pump management.

Patients currently treated with a rapid-acting insulin analog via CSII will be eligible for inclusion in the trial. All patients treated with insulin aspart or insulin glulisine at screening will be transferred to insulin lispro at Visit 2 so that all patients are using insulin lispro during the lead-in period. Patients must be using the MiniMed 530G, MiniMed 630G (US) or 640G (EU) insulin pump. The bolus delivery speed for all pumps will be set to standard speed (1.5 U/minute) for the duration of the lead-in and treatment phases of the study. The purpose of the lead-in period (prior to randomization) will be to obtain preliminary diagnostic tests, determine baseline hypoglycemia rate, and evaluate pump basal rates and bolus calculator settings (carb ratio [CR], insulin sensitivity factor [ISF], and active insulin time [AIT] for calculating mealtime and correction bolus doses) for appropriateness. During the study, patients will be expected to use the pump's bolus calculator to determine mealtime and correction bolus doses. Patients will be required to suspend use of personal CGM or FGM and the SmartGuard/Threshold Suspend feature of their pump, if applicable, during the lead-in and treatment phases of the study.

Dexcom G5 will be used by all patients in real-time mode beginning at Visit 2 and continuing throughout the treatment phase of the study. Dexcom G5 will allow patients to see real-time continuous glucose readings every 5 minutes and can aid in the identification of trends and patterns in glucose levels and detection of hyperglycemia and hypoglycemia. Patient interpretation of the Dexcom G5 data should be based on the glucose trends and several

sequential readings over time. All patients will be required to have the alerts and alarm features of Dexcom G5 enabled throughout the study.

Patients will be required to perform SMBG using the study-provided glucometer a minimum of 4 times/day, including pre-meal and bedtime, for calibration of the Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5) every 12 hours, and to confirm episodes of hypoglycemia, unexplained hyperglycemia, and the SMBG response to a correction bolus.

At every office visit, the date and time of each device used in the study (insulin pump, eCOA diary, glucometer, ketone meter, and CGM receiver) should be synchronized and verified by site staff.

At Visit 3 (Randomization Visit), patients will be randomly assigned to 1 of the 2 treatment sequences of double-blind LY900014 and insulin lispro. During Visit 3, under the observation of site staff, patients will insert a new CGM sensor and begin a new sensor session. Also under the observation of site staff, patients will fill a new pump reservoir and infusion set with investigational product (IP), insert the infusion set cannula into an appropriate pump site, and begin infusion of IP.

At Week 6 (Visit 6), patients will cross-over to the alternate treatment. Investigators will reset the patient's pump to the bolus calculator settings (CR, ISF, and AIT) and basal rates that had been optimized during the lead-in period. During the visit, under the observation of site staff, patients will insert a new CGM sensor and begin a new sensor session. Also under the observation of site staff, patients will fill a new pump reservoir and infusion set with IP, insert the infusion set cannula into an appropriate pump site, and begin infusion of IP.

During the treatment periods, patients and investigators will interact frequently and use SMBG and CGM data to optimize pump settings in order to maximize glycemic control.

The overall glycemic control goals for all patients enrolled in the study are similar to those recommended by the American Association of Clinical Endocrinologists (Bailey et al. 2016). The glycemic targets for this study are for patients to achieve a pre-prandial glucose level of approximately 100 mg/dL (5.6 mmol/L), a 1- to 2-hour PPG level of <180 mg/dL (<10.0 mmol/L), and a bedtime glucose level of approximately 90-130 mg/dL (5.0-7.2 mmol/L) with no hypoglycemia (defined as BG  $\leq$ 70 mg/dL [3.9 mmol/L]).

During the first 4 weeks of each treatment period, patients, in consultation with investigators, should use SMBG, CGM, and hypoglycemia data to adjust basal rates and bolus calculator settings (CR, ISF, and AIT) as necessary to meet the glycemic targets.

During the last 2 weeks of each treatment period, it is expected that CR, ISF, AIT, and basal rates would remain fairly stable, with adjustments if needed for safety reasons, such as hypoglycemia or unacceptable hyperglycemia. It is important to keep these as stable as possible, because CGM and hypoglycemia data from this period will be used for treatment comparisons.

Study governance considerations are described in detail in [Appendix 3](#).

[Figure ITSI.1](#) illustrates the study design.

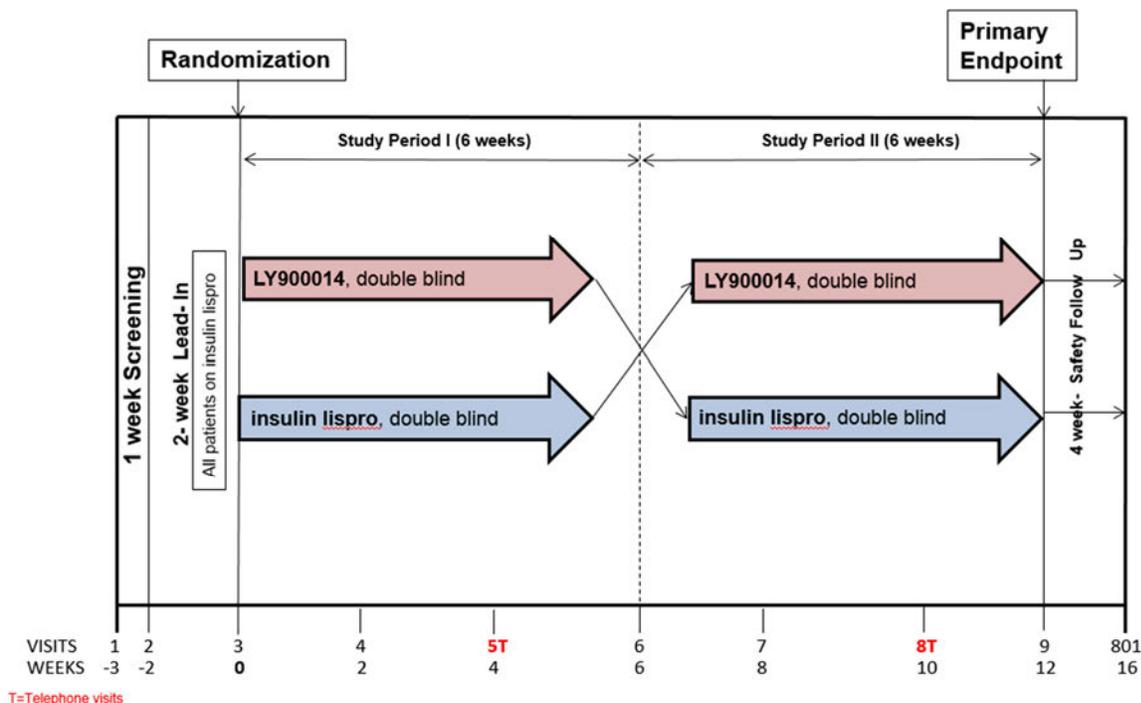


Figure ITSI.1. Illustration of study design for Clinical Protocol I8B-MC-ITSI.

## 5.2. Number of Participants

Approximately 60 participants will be screened to achieve 48 randomized patients for a total of approximately 42 patients to complete the study.

## 5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

## 5.4. Scientific Rationale for Study Design

A crossover design was chosen for this study to reduce variability and increase the power as each patient serves as his or her own control.

At the crossover point, patients are required to change their reservoir and infusion set, insert a new CGM sensor, and begin a new sensor session, and investigator will reset the patient's pump to the settings that had been optimized during the lead-in period. This avoids carryover effects on catheter occlusion-related treatment comparisons.

In addition, patients are encouraged to reach stable dose during the last 2 weeks of each period. This also minimizes carryover effect on the exploratory safety and efficacy outcomes.

## 5.5. Justification for Dose

Insulin lispro has been in the market for over 20 years with widespread use worldwide and has extensive efficacy and safety data. LY900014 will have the same insulin lispro concentration

(100 U/mL) as that of commercially available Humalog. The addition of treprostinil to the insulin lispro formulation does not modify the physical, chemical, or biological integrity of insulin lispro. The total serum insulin lispro exposure (area under the concentration curve from 0 to 5 hour postdose) are similar between LY900014 and insulin lispro in T1DM CSII. In addition, the total glucodynamic activity as measured in euglycemic clamp studies was similar between LY900014 and Humalog. In previous studies, these insulins were substituted unit for unit. The basal rates and bolus doses of insulins used in this study should be determined based on the individual needs of each patient.

## 6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Retests are also not allowed, except for cases when results are not available from the original sample.

### 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, based on the World Health Organization classification ([Appendix 5](#)) 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] Male patients:
  - a) No male contraception required except in compliance with specific local government study requirements.
- [4] 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 aged 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea

Or

- (3) a woman of 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 ([Appendix 6](#))
  - iv) test negative for pregnancy at the time of screening (Visit 1); note: a urine pregnancy test is conducted at Visit 3
- [5] Have been using CSII therapy for a minimum of 6 months prior to screening. Interruption of CSII is allowed once during the 6 months prior to screening for up to 14 consecutive days, such as during a hospitalization, a pump malfunction, or a “pump holiday”
- [6] Are currently treated with the same rapid-acting analog insulin (insulin lispro U-100, insulin aspart, or insulin glulisine) via CSII (where approved) for at least the last 30 days prior to screening
- [7] Have been using CGM or FGM (CGM preferred) for a total of at least 60 days during the 12 months prior to screening
- [8] Have HbA1c values  $\leq 8.5\%$ , as determined by the central laboratory at screening (Visit 1)
- [9] Have a body mass index (BMI) of  $\leq 35$  kg/m<sup>2</sup> at screening (Visit 1)
- [10] Are proficient, in the opinion of the investigator, in carbohydrate counting, and in adjusting basal rates and bolus calculator settings (CR, ISF, and AIT)
- [11] Are willing to take at least 3 meal-time insulin boluses every day on a regular basis throughout the trial
- [12] Are willing to use the pump’s bolus calculator (Bolus Wizard) to determine mealtime and correction bolus doses
- [13] Are willing to adhere to an infusion set and reservoir change interval of every 72  $\pm$  4 hours unless a change is required for failure of the infusion set
- [14] Are willing to perform SMBG, using the study glucometer, at least 4 times daily (including every 12 hours to calibrate the sensor), and to confirm hypoglycemia, unexplained hyperglycemia, and BG response following a correction bolus delivered via the pump
- [15] Are willing to use the Dexcom G5 Mobile Continuous Glucose Monitor in real-time mode throughout the study

- [16] Are willing to suspend use of personal CGM or FGM throughout the study
- [17] Are willing to suspend use of SmartGuard/Threshold Suspend throughout the study
- [18] Are willing to avoid use of all products containing acetaminophen or paracetamol while using the Dexcom CGM system
- [19] Must be using a MiniMed 530G or 630G (US) or 640G (EU) insulin pump for at least the last 30 days and willing to stay on the same pump throughout the study (pump must be approved for use in the country where the patient resides)
- [20] Must use study-provided MiniMed insulin pump reservoirs and Mio infusion sets
- [21] Are willing to keep records in eCOA devices as required by this protocol
- [22] Have access to a telephone, or alternative means for close monitoring and communications, and have access to a reliable cellular signal or wireless internet access for transmission of the eCOA data
- [23] Have refrigeration in the home or have ready access to refrigeration for storage of insulin

### **Informed Consent**

- [24] 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**

- [25] Have hypoglycemia unawareness as judged by the investigator
- [26] Have had more than 1 episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) within 6 months prior to screening
- [27] Have had more than 1 emergency room visit or hospitalization due to poor glucose control (hyperglycemia or DKA) within 6 months prior to screening
- [28] Have significant insulin resistance defined as having received a total daily dose of insulin  $>1.2$  U/kg at the time of screening (Visit 1), as determined by the average total daily insulin dose over the 3 days prior to screening divided by weight in kilograms based on investigator review of the patient's pump history
- [29] Have significant lipohypertrophy, lipoatrophy, or scars within the subcutaneous tissue in areas of infusion, in the opinion of the investigator
- [30] Have a history of abscess at an infusion site within the last 90 days prior to screening

- [31] Have a history within the past 6 months of changing their pump infusion set more frequently than every 3 days on a regular basis
- [32] Have vision loss or hearing loss that does not allow recognition of pump screens, alerts, and alarms
- [33] Have presence of clinically significant gastrointestinal disease (for example, clinically active gastroparesis associated with wide glucose fluctuations; in the investigator's opinion) or gastric bypass.
- [34] 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
- [35] 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 ([Appendix 7](#)), myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft
- [36] Renal:
- History of renal transplantation
  - Currently receiving renal dialysis
  - Serum creatinine  $>2.0$  mg/dL ( $177$   $\mu\text{mol/L}$ ) at screening (Visit 1) as measured by the central laboratory
- [37] 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 (Visit 1)
  - Total bilirubin level (TBL)  $\geq 2X$  the upper limit of normal (ULN) (with the exception of Gilbert's disease) as defined by the central laboratory Or
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $\geq 3X$  ULN as defined by the central laboratory
- [38] 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
- [39] Have any hypersensitivity or allergy to any of the insulins or excipients used in this trial
- [40] Hematologic: have had a blood transfusion or severe blood loss within 90 days prior to screening or have known hemoglobinopathy, anemias, or any other traits known to interfere with measurement of HbA1c

**Prior/Concomitant Therapy**

- [41] Have used insulin human inhalation powder (Afrezza®) within 90 days prior to screening
- [42] Are receiving any oral or injectable medication intended for the treatment of diabetes mellitus other than rapid-acting analog insulin via CSII in the 90 days prior to screening. Occasional pen or syringe injection of insulin is allowed in the event of pump malfunction, unexplained hyperglycemia not responsive to pump correction bolus, etc.
- [43] Glucocorticoid therapy: are receiving chronic (lasting longer than 7 consecutive days) systemic glucocorticoid therapy (including intravenous, IM, subcutaneous, and oral) or intra-articular, but excluding topical, intraocular, intranasal, and inhaled preparations), or have received such therapy within 8 weeks immediately prior to screening with the exception of replacement therapy for adrenal insufficiency

**Prior/Concurrent Clinical Trial Experience**

- [44] Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study
- [45] Have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed
- [46] Have previously completed or withdrawn from this study after having signed the informed consent form (ICF) or any other study investigating LY900014 after receiving at least 1 dose of the IP

**Other Exclusions**

- [47] Have an irregular sleep/wake cycle (for example, patients who sleep during the day and work during the night)
- [48] 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
- [49] Are Lilly employees or representative (including employees, temporary contract workers, or designees responsible for the conduct of the study)
- [50] Are unable and/or unwilling to provide informed consent, to make themselves available for the duration of the study, or to abide by study procedures

### **6.3. Lifestyle Restrictions**

Study participants 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 study.

### **6.4. Screen Failures**

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Retests are also not allowed, except for cases when results are not available from the original sample.

## 7. Treatments

### 7.1. Treatments Administered

This study involves a comparison of LY900014 and insulin lispro with mealtime boluses administered 0 to 2 minutes prior to the start of the meal. Patients will fill pump reservoirs from blinded vials with each infusion set change (that is, every  $72 \pm 4$  hours). [Table ITSI.3](#) shows the treatment regimens.

**Table ITSI.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; basal infusion rates throughout 24 hours a day; correction boluses as necessary
Insulin lispro	100 U/mL	Individualized dosing	CSII	Mealtime bolus 0-2 min prior to start of the meal; basal infusion rates throughout 24 hours a day; correction boluses as necessary

Abbreviation: CSII = continuous subcutaneous insulin infusion.

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

- Explaining the correct use of IP to the patient
- Explaining storage requirements for IP to the patient
- Explaining requirements for recording date, time, and amount of correction 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 that all unused medications are 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 country's regulatory requirements. Study insulins (LY900014 and insulin lispro) 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 insulin lispro.

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

### **7.1.2. Insulin Pumps**

Patients will use their personal MiniMed 530G or 630G (US) or MiniMed 640G (EU) pump throughout the study, but will be required to use the reservoirs and infusion sets provided by the investigative site. MiniMed reservoirs and Mio infusion sets with 6-mm cannula and 23-inch tubing will be provided to all patients. The Mio infusion set was chosen because of its all-in-one design that combines the infusion set with the inserter device. All patients' pumps will be set to deliver boluses at standard speed (1.5 U/minute) for the duration of the lead-in and treatment phases of the study.

### **7.1.3. Method of Treatment Assignment**

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

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

Sequence A: LY900014 → insulin lispro

Sequence B: insulin lispro → LY900014

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

Patients will fill a new pump reservoir and infusion set with IP, then insert a new pump infusion set cannula into an appropriate site, and begin infusion of IP prior to leaving the investigative site at Visits 2, 3, and 6. Patients will continue to fill reservoirs and infusion sets with IP and insert a new infusion set cannula into an appropriate site every  $72 \pm 4$  hours as outpatients, unless a change is required for failure of the infusion set.

The IWRS will be used to assign all IP during the study, including insulin lispro during the lead-in period. The IWRS will be used to assign vials containing double-blind IP to each patient randomized to the sequence of treatment groups. Site personnel will confirm that they have located the correct vials by entering a confirmation number found on the vials into the IWRS.

### **7.1.4. Selection and Timing of Doses**

#### **7.1.4.1. Target Glucose Values for Titration of Insulin Therapy**

All patients not currently using insulin lispro in their pumps will begin using insulin lispro at the beginning of the 2-week lead-in period. Patients, in consultation with investigators, will be encouraged to adjust pump settings during the first 4 weeks of each treatment period with the goal of achieving glycemic targets so that these settings are fairly stable during the last 2 weeks of each period.

The glycemic targets for patients in this study are listed in [Table ITSI.4](#).

**Table ITSI.4. Target Glucose Values for Adjustment of Insulin Therapy**

Time of Target Glucose Measurement	Self-Monitored Blood/Interstitial Glucose Target (Range)
Pre-prandial	Target: 100 mg/dL or 5.6 mmol/L Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
1- to 2-hour postprandial	Target: <180 mg/dL or 10.0 mmol/L
Bedtime	Range: 90 to <130 mg/dL or 5.0 to 7.2 mmol/L with no hypoglycemia (defined as BG $\leq$ 70 mg/dL [3.9 mmol/L])

Abbreviations BG = blood glucose.

#### 7.1.4.2. Insulin Titration

The treatment goals for patients of this study are to achieve a preprandial glucose level of approximately 100 mg/dL (5.6 mmol/L), a 1- to 2-hour PPG level of <180 mg/dL (10.0 mmol/L), and a bedtime glucose level of approximately 90 to 130 mg/dL (5.0 to 7.2 mmol/L) with no hypoglycemia (defined as BG  $\leq$ 70 mg/dL [3.9 mmol/L] [Bailey et al. 2016]). Adjustment of pump settings to optimize basal rates and bolus dose calculation factors are determined by the investigator in discussion with the patient. Additional discussion between visits may be required to enable the patient to reach the target BG values shown in [Table ITSI.4](#).

#### 7.1.4.3. Transitioning off Study Insulin Therapy

At Visit 9 or Early Discontinuation, patients should resume their pre-randomization pump basal rates and bolus calculator settings and start a non-study rapid-acting insulin analog via CSII.

## 7.2. Blinding

This is a double-blind study in which the treatment groups, LY900014 and insulin lispro, will have basal rates and 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 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 (CRP)/clinical research scientist (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.

### 7.3. Dosage Modification

See section [7.1.4](#).

### 7.4. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for confirming that 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, 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).

### 7.5. Treatment Compliance

The investigator or designee will assess compliance of the patient at each visit, based on a review of the patient's pump and CGM downloads, glycemic control, adherence to the visit and treatment schedule, and completion of the patient's eCOA. 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 the study. No specific study data will be collected to analyze treatment compliance.

### 7.6. Concomitant Therapy

Guidance on restrictions for concomitant therapies is provided in [Table ITSI.5](#).

**Table ITSI.5. Concomitant Medications**

<b>Drug Class</b>	<b>Acute Use</b>	<b>Chronic Use</b>	<b>Safety Follow-up Periods</b>	<b>Conditions for Use</b>
Systemic glucocorticosteroid (including IM, IV, SC, and oral) or intra-articular <sup>a</sup> except in the case of replacement therapy for adrenal insufficiency	No	No	No	
Afrezza® (inhaled insulin)	No	No	No	
Any oral or injectable medication intended for the treatment of diabetes mellitus other than rapid-acting analog insulin via CSII	Yes	No	Yes	In the event of interruption of CSII, such as for pump failure or hospitalization, injection of prandial and/or basal insulin will be allowed for up to 7 days during each of the 6-week treatment periods until CSII can be resumed
Acetaminophen- or paracetamol-containing medications	No	No	Yes	

Abbreviations: CSII = continuous subcutaneous insulin infusion; IM = intramuscular; IV = intravenous; SC = subcutaneous.

Note: According to country labeling.

<sup>a</sup> Topical, inhaled, intraocular, or intranasal steroid preparations are allowed.

## **7.7. Treatment after the End of the Study**

### **7.7.1. Continued Access**

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

### **7.7.2. Special Treatment Considerations**

After discontinuation of IP at the end of the treatment period or earlier, randomized patients should start a non-study rapid-acting analog insulin via CSII.

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

## 8. Discontinuation Criteria

### 8.1. Discontinuation from Study Treatment

Patients who need to discontinue from study treatment will also be discontinued from the Study. Please refer to Section 8.2.

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

If the sponsor or investigator identifies 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 on study treatment. If the investigator and the sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled patient to continue in the study with IP. Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

### 8.2. Discontinuation from the Study

Patients will be discontinued 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
- The patient becomes pregnant
- If an investigator, study site personnel performing assessments, or patient is unblinded, the patient must discontinue IP
- Frequent use of prohibited concomitant medication
- Use of pump that is not allowed
- Defiant continued use of SmartGuard/Threshold Suspend technology
- The patient has not used IP for more than 7 consecutive days
- Enrollment in any other clinical study 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)
- Investigator decision

- the investigator decides that the patient should be discontinued from the study
- if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Subject decision
  - the patient requests to be withdrawn from the study
- **Discontinuation due to a hepatic event or liver test abnormality:** patients who are discontinued due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via electronic case report form (eCRF).

Discontinuation 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 international normalized ratio >1.5
- 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 >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol, with the exception of those who discontinue during the lead-in period will not need to have laboratory tests drawn.

### 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 eCRF.

Lilly personnel will not be involved in any attempts to collect vital status information.

## 9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, 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. Safety Assessments

#### 9.1.1. Primary Assessments

The rate of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump.

#### 9.1.2. Secondary Assessments

- The incidence of infusion set failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump
- Rate and incidence of premature infusion set changes by reason (infusion set kinked, came out, or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other)
- Time interval until infusion set change (overall and due to any suspected infusion set occlusion)
- Bolus, basal, and total insulin dose (units and units/kg) and bolus/total insulin ratio
- Interstitial glucose reduction from hyperglycemia following a non-meal-related correction bolus delivered via the pump
- Rate of severe hypoglycemia

#### 9.1.3. Appropriateness of Assessments

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

#### 9.1.4. Study Procedures

##### 9.1.4.1. Electronic Clinical Outcomes Assessment

The eCOA diary will wirelessly receive all glucose data directly from the study BG meter, thereby increasing the validity of measures reported by the patient and minimizing transcription

errors in recording the measures. The use of e-diaries should also allow more complete and accurate capturing of infusion set change data, hypoglycemic events, suspected infusion set occlusion (unexplained hyperglycemia that leads to infusion set change), correction boluses, as well as more frequent and timely interactions between investigator and patients as the intensity of their individual diabetes management increases.

Physicians and designated clinical staff will have access via the eCOA portal (secured web-based site) to BG readings, infusion set change data, hypoglycemic events, suspected infusion set occlusions, and correction boluses for each patient once transferred. It is recommended that investigators review patient data via the eCOA portal at least once weekly for clinical decision making and safety monitoring. More frequent reviews may be necessary for individual patient management.

An instruction manual will be provided to patients and investigative sites. Additional instruction and training will be provided to the investigative sites regarding data collection, review, retention, and archival processes. In the event of eCOA malfunction or loss, the patient will be instructed to immediately contact the investigative site for instructions regarding replacement of the equipment.

#### **9.1.4.1.1. Correction Boluses**

Patients will be instructed to enter the date, time, and dose for all non-meal-related correction bolus doses (those not associated with a meal or combined with a meal bolus) into the eCOA diary. This information is critical data for evaluating the primary objective of the study.

#### **9.1.4.1.2. Infusion Set Changes**

The eCOA system will be used by patients to collect all infusion set changes, including date and time of change, designation of routine or premature change, primary reason for premature change (infusion set kinked, came out, or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other).

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

Investigators will review pump occlusion alarms, suspected infusion set occlusions, and premature infusion set changes with patients at each visit.

Any interruption of CSII will need to be documented in the eCRF. When patients resume use of pump following the interruption, the infusion set insertion should be entered as “routine” infusion set change in eCOA.

#### **9.1.4.1.3. Hypoglycemia**

Hypoglycemic events will be captured throughout the clinical study in eCOA along with date and time of the BG level if measured and hypoglycemia treatment and outcome data.

**9.1.4.1.4. Self-Monitoring Blood Glucose**

Patients will be instructed to perform SMBG according to the schedule of activities. SMBG values are expected for mealtime bolus calculations and are required for calibrating Dexcom G5 every 12 hours, and for confirming episodes of hypoglycemia, unexplained hyperglycemia, and the glucose response to a correction bolus.

**9.1.4.1.4.1. Four-Point Self-Monitoring Blood Glucose**

Patients should be instructed to measure a minimum of 4 SMBG readings daily (consists of fasting [pre-morning meal], pre-midday meal, pre-evening meal, and pre-bedtime), with additional readings as needed for glucose self-management.

Site personnel may request additional SMBG from patients and/or assess SMBG values at other times for clinical decision-making. Missing values in 4-point SMBG profiles will not be considered protocol deviations unless, in the opinion of the investigator, they are excessive and reflect noncompliance with the protocol.

**9.1.4.2. Troubleshooting Unexplained Hyperglycemia**

Investigators will review unexplained hyperglycemia troubleshooting and management with patients at Visit 2 and may repeat as necessary at subsequent visits. Troubleshooting guidelines for unexplained hyperglycemia management will be provided as a tool for patient use. A blood ketone meter and test strips will be provided to each patient to aid in hyperglycemia management. All episodes of unexplained hyperglycemia >250 mg/dL should be confirmed by SMBG using the study glucometer. Patients should check to ensure the pump is in place, the prior bolus dose was delivered, and the infusion set is in place without any leaks or kinks in the system. All non-meal-related correction boluses including date, time, and dose should be entered into eCOA. Glucose response to the correction bolus should be confirmed by SMBG in approximately 1 hour. Blood ketones should be tested with the meter provided when unexplained hyperglycemia occurs with blood glucose >250 mg/dL (13.9 mmol/L) or a pump occlusion alarm occurs with blood glucose >250 mg/dL (13.9 mmol/L). If blood ketones are positive (>0.6 mmol/L) or nausea and/or vomiting is present, the patient should inject the correction dose by syringe, change the insulin, reservoir, and infusion set, and continue to monitor BG every 1 to 2 hours until within range. If BG is not responding to correction and/or signs of DKA are present, the patient should go immediately to the nearest emergency room.

**9.1.4.3. Continuous Glucose Monitoring**

The Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5) will be used by all patients in real-time mode beginning at Visit 2 and continuing throughout the treatment phase of the study. 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 Mobile System including expectations for completion of the following daily requirements:

- Strive to eat a similar breakfast each day to the extent possible and to avoid snacking for the 2-hour period after breakfast unless it is necessary to treat hypoglycemia.
- Enter a Carbs Event marker at the start of the breakfast meal into the Dexcom receiver.
- Enter an insulin Event marker at the time of the breakfast meal bolus into the Dexcom receiver.

- Keep the Dexcom Receiver close to the body or within about 6 meters (about 20 feet) of the Dexcom Transmitter, without obstruction, to minimize the loss of transmitted data.
- Calibrate the CGM 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 CGM System.

The CGM data will be downloaded at every site visit for clinical decision-making and transmitted to secure cloud storage for retrospective analysis.

#### **9.1.4.4. Diabetes Education and Nutritional Counseling**

Initial training at Visit 2 will include diabetes education and nutrition counseling. Training will include a review of correct pump use (frequency of reservoir and infusion set changes, priming of the infusion set, infusion site rotation) and review patient's ability to carb count, use the pump's bolus calculator to determine bolus and correction doses, use bolus types appropriately, treat hypoglycemia, etc. Appropriate site personnel will administer training and education using locally approved diabetes education/training materials and programs or by using other materials that may be provided by the sponsor. Patients may be provided additional training and education at visits following Visit 2, based upon patient needs.

## **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 of 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 following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the patient to discontinue the IP before completing the study. The patient should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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 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
- Severe hypoglycemic events: episodes of severe hypoglycemia as determined by the investigator according to the definition provided in Section 9.4.2 must be reported as SAEs

All AEs occurring after signing the ICF are recorded in the case report form (CRF) and assessed for serious criteria. The SAE reporting to the sponsor 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 as per SAE reporting requirements and timelines (see Section 9.2.1) 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 adverse event should have additional data collected using the eCRF.

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 subjects once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/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 to ensure the safety of study participants, monitor quality, and 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.

### 9.2.2.1. Device Complaint Handling

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with Dexcom G5 so that the situation can be assessed. Any Dexcom G5 complaint should be reported per the manufacturer's label instructions. Contact information will be provided to the investigative site personnel in the event that either personnel or patients have questions or complaints regarding Dexcom G5.

## 9.3. Treatment of Overdose

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

## 9.4. Safety

### 9.4.1. Hypoglycemia

Patients are encouraged to perform SMBG whenever hypoglycemia may be suspected, either by symptoms experienced or 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 level  $\leq 70$  mg/dL (3.9 mmol/L) as hypoglycemia.

Hypoglycemic events will be collected in eCOA. If a hypoglycemic event is suspected, the patient should record the BG value, any associated symptoms, and the treatment administered in eCOA. The patient should contact the site as necessary. Reports of hypoglycemia will be classified by the investigator as "severe" or "not severe" based upon data collected in eCOA and in consultation with the patient (see below and in Section 9.4.2). All episodes of severe hypoglycemia will be reported as AEs via electronic data entry and also as SAEs.

Hypoglycemia will be described using the following definitions:

- **Documented Glucose Alert; BG  $\leq 70$  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. BG 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  $\leq$ 70 mg/dL [3.9 mmol/L]).

- **Other Hypoglycemia**
  - **Nocturnal Hypoglycemia:** any documented hypoglycemic event (including severe hypoglycemia) that occurs between bedtime and waking.
  - **Relative Hypoglycemia (also referred to as Pseudohypoglycemia [Seaquist et al. 2013]):** an event during which typical symptoms of hypoglycemia occur that do not require the assistance of another person, are accompanied by BG  $>$ 70 mg/dL (3.9 mmol/L). Patients may report symptoms of hypoglycemia before their BG concentration falls below 70 mg/dL (3.9 mmol/L). Events with BG  $\leq$ 70 mg/dL should not be categorized as relative hypoglycemia.
  - **Probable Symptomatic Hypoglycemia:** an event during which symptoms are present, but BG measurement was not reported.
  - **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, ECGs should be performed at Visit 1 according to the study-specific described in the Schedule of Activities (Section 2).

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) 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).

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

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. Immunogenicity Assessments**

Blood samples will be collected as specified in the Schedule of Activities (Section 2) for the assessment of anti-insulin lispro antibodies; this assessment will be performed using a validated assay at a laboratory approved by the sponsor.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ethical review boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY900014. Any samples remaining after 15 years will be destroyed.

#### **9.4.7. Pump Occlusion Alarms and Suspected Pump Occlusions**

Patients will document all pump infusion set changes in eCOA and designate if the change was routine or premature. Patients will select whether the early infusion set change was due to an infusion set failure (kinked, came out, leaking), infusion site complication (pain or redness), empty pump reservoir, pump occlusion alarm, other, or if the early infusion set change was due to a suspected infusion set occlusion defined as unexplained hyperglycemia. In the latter case, patients will choose or add a new correction bolus from the eCOA diary that corresponds to the timing of the suspected infusion set occlusion. They will then indicate if the correction bolus was given via pump or via syringe. Investigators will review pump occlusion alarms and suspected pump occlusions with patients at each visit.

#### **9.4.8. Safety Monitoring**

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

##### **9.4.8.1. Hepatic Safety Monitoring**

If a study patient experiences elevated ALT  $\geq 3X$  ULN, ALP  $\geq 2X$  ULN, or elevated TBL  $\geq 2X$  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  $\geq 5X$  ULN on 2 or more consecutive blood tests
- Elevation of serum TBL to  $\geq 2X$  ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to  $\geq 2X$  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. Biomarkers**

Not applicable.

**9.9. Health Economics**

Not applicable.

## 10. Statistical Considerations

### 10.1. Sample Size Determination

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

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

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

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

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

### 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.

Safety analyses will be conducted on the Safety Population. Analyses of AEs (including DKA) will include all data collected during the course of the entire 6-week treatment period for each treatment group regardless of IP use. Analyses of hypoglycemia will be conducted on data collected prior to permanent discontinuation (i.e. last dose) of IP in each 6-week treatment period. Unless otherwise specified, pump-related safety analyses (infusion set failures,

premature infusion set changes, time interval until infusion set change, and interstitial glucose reduction rate) will exclude data (if any) that are collected while patients temporarily are off pump or off IP. Data collected during the safety follow-up period will not be used for comparisons between treatment groups.

Exploratory efficacy analyses (e.g., 1,5 AG and HbA1c) will be conducted on all randomized patients according to the treatment the patients are assigned to and CGM analyses will be conducted on the CGM Population.

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

Treatment group comparisons will be performed for the primary objective (Section 10.3.3.1) at the full significance level of 0.05. No multiplicity adjustment will be made for secondary and exploratory objectives.

Baseline is defined as the last nonmissing measurement at or before the randomization visit (Visit 3), unless otherwise specified.

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

- MMRM Model 1: for analysis of variables that are measured at multiple designated visits within each randomized treatment period (e.g. weight and vital signs), the model will include the fixed class effects of treatment, period, sequence, strata (region, historical use of SmartGuard/Threshold Suspend, HbA1c), week (relative to the start of each randomized treatment period), and week-by-treatment interaction, and the continuous, fixed covariate of baseline value. If the analysis fails to converge, the following covariance structures will be tested in order:
  - Compound symmetry with heterogeneous variances
  - Compound symmetry without heterogeneous variances
- MMRM Model 2: for analysis of variables that are only measured once for each randomized treatment period (e.g., 1,5 AG), the model will include the fixed class effects of treatment, period, sequence, strata (region, historical use of SmartGuard/Threshold Suspend, HbA1c), and the continuous, fixed covariate of baseline value (Grizzle 1965). If the analysis fails to converge, a covariance structure of compound symmetry without heterogeneous variances will be used.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

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

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

### **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 overall and by treatment sequence and period. Reasons for discontinuation from the study during Period I and Period II will be summarized by treatment sequence and period.

Reasons for discontinuation from the study during the lead-in and follow-up periods will be summarized for overall population.

#### **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 and by treatment sequence. Summary statistics will include sample size, mean, SD, median, minimum, and maximum for continuous measures and sample size, frequency, and percent for categorical measures. Baseline diabetes characteristics will be summarized in a similar manner.

Medical history and AEs at baseline will be summarized by preferred term (PT) within system organ class (SOC).

#### **10.3.2.3. Concomitant Therapy**

The type of rapid-insulin therapy at study entry will be summarized by treatment sequence. The basal and bolus insulin doses during the lead-in period will be also be summarized by treatment sequence.

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

#### **10.3.2.4. Treatment Compliance**

No specific study data will be collected for analysis of treatment compliance (as defined in Section 7.5). No analyses are planned to assess treatment compliance.

### 10.3.3. Safety Analyses

#### 10.3.3.1. Primary Analyses

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

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

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

If more than 1 non-meal-related correction bolus is given for an unexplained hyperglycemia, only the first correction bolus time will be used to determine the 1 hour (+10 minutes) timeframe following the correction bolus as described in Section [\(9.1.4.1.1\)](#).

The infusion set failure rate (events/patient/30 days) will be derived for each patient for the lead-in, Period I, and Period II, and summarized by treatment sequence.

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

#### 10.3.3.2. Secondary Analyses

The incidence (percent of patients with at least 1 event) of infusion set failures, as defined in the primary objective, premature infusion set changes by reason, and severe hypoglycemia will be analyzed using Prescott's exact test.

Similarly, Wilcoxon signed-rank test will be used to analyze the rate of infusion set failures, premature infusion set changes by reason, and severe hypoglycemia, as described in Section [10.3.3.1](#).

As an additional analysis, the rate and incidence will be determined for infusion set failures leading to premature infusion set changes due to unexplained hyperglycemia with blood glucose >250 mg/dL that does not decrease by >50mg/dL within 1 hour following a correction bolus delivered via the pump and analyzed in the same way as described for the primary endpoint.

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

Other safety measures will include AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro. Analyses will be performed on data collected over the 6-week treatment period for each treatment group.

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.

Serious adverse events, 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 1 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 Prescott's test. SAEs, AEs reported as reason for discontinuation from the study, and TEAEs will also be summarized for open-label insulin lispro during the lead-in period.

If there are  $\geq 10$  patients with severe hypoglycemic event, the proportion of patients with at least 1 severe hypoglycemic event (incidence) after randomization will be analyzed using a generalized linear mixed model with options of the binomial distribution and logit link function. The model will include treatment, period, and sequence. The within-patient error will be modeled as the compound symmetry variance-covariance matrix. Prescott's exact test will be conducted as sensitivity analyses.

Both date and time of all infusion set changes will be captured and time interval until infusion set change will be derived through a minute-to-hour conversion.

The interstitial glucose reduction rate within 4 hours following a non-meal-related correction dose will be calculated by dividing the interstitial glucose reduction by the time it takes to recover ( $<180$  mg/dL) from hyperglycemia after the correction dose. If within 4 hours a second correction bolus is given, only the first non-meal-related correction bolus time will be used. If the glucose never recovers to  $<180$  mg/dL within 4 hours, the glucose rate will be calculated by dividing the greatest glucose reduction within 4 hours by the time it takes to reach this level.

The glucose reduction rate will be analyzed by a MMRM model. The MMRM model will include the fixed effects of treatment, period, and sequence as fixed effects and patient as a random effect. The interstitial glucose reduction rate will also be analyzed by sub-intervals of interstitial glucose levels at the time of the non-meal-related correction bolus: 180 to 250, 250 to 300, and >300 mg/dL (10 to 13.9, 13.9 to 16.7, and >16.7 mmol/L).

Actual and change from baseline in basal, bolus, and total dose, as well as the bolus/total insulin dose ratio, will be analyzed by a MMRM model as described in Section 10.3.1.

As described in Section 10.3.1, continuous safety variables (for example, time interval until infusion change), as well as the change from baseline for these variables (if applicable), will be analyzed by the MMRM models, and categorical variables will be analyzed using Prescott's exact test for treatment comparisons unless otherwise specified.

Details for assessing immunogenicity data will be described in the SAP. No statistical comparisons between treatment groups will be conducted for immunogenicity data because patients will be exposed to both LY900014 and insulin lispro due to the crossover design.

#### **10.3.3.3. Tertiary/Exploratory Analyses**

Continuous variables and the change from baseline for these variables will be analyzed by the MMRM models as described in Section 10.3.1. Categorical variables will be analyzed either by model (for example, a generalized linear mixed model) or nonparametric methods (for example, Wilcoxon signed-rank test or Prescott's exact test).

To assess the glucose control over the course of approximately 72-hours of continuous infusion, the duration and percentage of time in ranges (target, hypoglycemia or hyperglycemia) and incremental AUCs after breakfast, will be derived based upon the CGM raw data collected on Day 1, Day 2, and Day 3 of infusion set catheter wear and summarized by treatment group.

Analysis details for the tertiary endpoints will be described in the SAP.

#### **10.3.3.4. Subgroup Analyses**

The following subgroups will be explored to evaluate consistency of treatment effects on the primary safety measure:

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

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

Additional exploratory subgroup analyses may also be performed.

#### **10.3.4. Efficacy Analyses**

Efficacy data will be evaluated as exploratory objectives. Analysis details will be described in the SAP.

### ***10.3.5. 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.

## 11. References

- Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;15(7):539-553.
- Bailey TS, Grunberger G, Bode BW, Handelsman Y, Hirsch IB, Jovanović L, Roberts VL, Rodbard D, Tamborlane WV, Walsh J; American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE). American Association of Clinical Endocrinologists and American College of Endocrinology 2016 outpatient glucose monitoring consensus statement. *Endocr Pract.* 2016;22(2):231-261. Erratum in: *Endocr Pract.* 2016;22(4):516.
- Bennett P. Classification and diagnosis of diabetes mellitus and impaired glucose tolerance. In: Pickup JC, Williams G, editors. *Textbook of diabetes*. Vol. 1. 1st ed. Oxford: Blackwell Scientific Publications; 1991:p 37-44.
- Grizzle JE. The two-period change-over design and its use in clinical trials. *Biometrics.* 1965;21:467-480.
- [PMR] Pharmaceutical and healthcare market in CEE and CIS. Remodulin approved in 22 European countries, also Poland. PMR web site. Available at <http://www.cee-pharma.com/news/25318/remodulin-approved-in-22-european-countries-also-poland>. Published September 1, 2005. Accessed September 16, 2016.
- Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corp; 2014.
- Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care.* 2013;36(5):1384-1395.
- Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care.* 2013;36(8):2271-2279.
- Thrasher J, Surks H, Nowotny I, Rotthaeuser B, Wernicke-Panten K, Garg S. Assessment of the safety of SAR342434 and Humalog when administered through insulin pump-pilot study [poster]. In: American Diabetes Association 77th Scientific Sessions; Jun 9-13, 2017; San Diego (CA). Poster nr 1042-P.

## 12. Appendices

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## Appendix 1. Abbreviations and Definitions

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Term	Definition
<b>AE</b>	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 AE 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.
<b>AIT</b>	active insulin time
<b>ALP</b>	alkaline phosphatase
<b>ALT</b>	alanine aminotransferase
<b>AST</b>	aspartate aminotransferase
<b>BG</b>	blood glucose
<b>blinding</b>	<p>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.</p> <p>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.</p>
<b>BMI</b>	body mass index
<b>CGM</b>	continuous glucose monitoring
<b>CI</b>	confidence interval
<b>confirmed pump occlusion</b>	An interruption in continuous pump insulin flow that triggered an occlusion alarm that would not clear, after confirming that the pump and infusion set are in place without leaks or kinks in the system.
<b>CR</b>	carb ratio
<b>CRF</b>	case report form
<b>CRP/CRS</b>	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.
<b>CSII</b>	continuous subcutaneous insulin infusion
<b>CSR</b>	clinical study report
<b>DKA</b>	diabetic ketoacidosis

<b>ECG</b>	electrocardiogram
<b>eCOA</b>	electronic clinical outcomes assessment
<b>eCRF</b>	electronic case report form
<b>enroll</b>	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.
<b>enter</b>	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>ERB</b>	ethical review board
<b>FDA</b>	Food and Drug Administration
<b>FGM</b>	flash glucose monitoring
<b>GCP</b>	good clinical practice
<b>HbA1c</b>	hemoglobin A1c
<b>IB</b>	Investigator's Brochure
<b>ICF</b>	informed consent form
<b>ICH</b>	International Conference on Harmonisation
<b>IP</b>	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 in 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.
<b>ISF</b>	insulin sensitivity factor
<b>IWRS</b>	interactive web-response system
<b>LLT</b>	lowest level term
<b>LS</b>	least squares
<b>MDI</b>	multiple daily injections
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>MMRM</b>	mixed-effect model repeated measure
<b>PPG</b>	postprandial glucose
<b>product complaint</b>	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.
<b>PT</b>	preferred term
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>screen</b>	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.
<b>SD</b>	standard deviation
<b>SMBG</b>	self-monitored blood glucose
<b>SOC</b>	system organ class
<b>SUSARs</b>	suspected unexpected serious adverse reactions
<b>T1DM</b>	type 1 diabetes mellitus
<b>T2DM</b>	type 2 diabetes mellitus
<b>TBL</b>	total bilirubin level
<b>TEAE</b>	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 does not necessarily have to have a causal relationship with this treatment.
<b>ULN</b>	upper limit of normal
<b>unexplained hyperglycemia</b>	High blood glucose 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 (for example, kinked, came out, leaking), or an infusion site complication (for example, pain, redness).

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## Appendix 2. Clinical Laboratory Tests

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### Clinical Laboratory Tests<sup>a</sup>

<b>Hematology</b>	<b>Clinical Chemistry(Serum Concentrations of)</b>
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
	Total protein
	Glucose
	Albumin
	Creatinine kinase (CK)
	1,5 Anhydroglucitol
	Hemoglobin A1c
	<b>Stored Samples</b>
	Anti-insulin lispro antibodies
<b>Urinalysis</b>	
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Blood	
Urine leukocyte esterase	
Bilirubin	
Nitrite	
<b>Serology</b>	
Pregnancy test (females only) <sup>b</sup>	
Follicle-stimulating hormone <sup>c</sup>	

Abbreviations: IP = investigational product; 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 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.
- c 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.

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**Appendix 3. Study Governance Considerations**

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## **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 nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- Ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of 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 study.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

### ***Appendix 3.1.2. Recruitment***

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

### ***Appendix 3.1.3. Ethical Review***

The investigator or an appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the 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 GCP.

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

- The protocol and related amendments and addenda, current IB, and updates during the course of the study,
- ICF
- Other relevant documents (for example, curricula vitae, advertisements)

**Appendix 3.1.4. Regulatory Considerations**

This study will be conducted in accordance with the protocol and with the:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences 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 3.1.5. Investigator Information**

Physicians with a specialty in endocrinology or primary care physicians specializing in endocrinology or internal medicine will participate as investigators in this clinical trial.

**Appendix 3.1.6. 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 3.1.7. Final Report Signature**

The 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 CRF), 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***

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic clinical outcomes assessment measures (for example, a rating scale) or other data reported directly by the patient (for example, daily dosing schedule, event diary) are entered into an eCOA instrument (for example, personal digital assistant, or by means of IWRS) at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

If eCOA records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. 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.

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

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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

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#### Hepatic Hematology<sup>a</sup>

Hemoglobin  
 Hematocrit  
 RBC  
 WBC  
 Neutrophils, segmented  
 Lymphocytes  
 Monocytes  
 Eosinophils  
 Basophils  
 Platelets

#### Hepatic Chemistry<sup>a</sup>

Total bilirubin  
 Direct bilirubin  
 Alkaline phosphatase  
 ALT  
 AST  
 GGT  
 CPK

#### Haptoglobin<sup>a</sup>

#### Hepatic Coagulation<sup>a</sup>

Prothrombin time  
 Prothrombin time, INR

#### Hepatic Serologies<sup>a,b</sup>

Hepatitis A antibody, total  
 Hepatitis A antibody, IgM  
 Hepatitis B surface antigen  
 Hepatitis B surface antibody  
 Hepatitis B core antibody  
 Hepatitis C antibody  
 Hepatitis E antibody, IgG  
 Hepatitis E antibody, IgM

#### Anti-nuclear Antibody<sup>a</sup>

#### Alkaline Phosphatase Isoenzymes<sup>a</sup>

#### Anti-smooth Muscle Antibody (or Anti-actin Antibody)<sup>a</sup>

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

<sup>a</sup> Assayed by Lilly-designated or local laboratory (if test results are required urgently to manage patient care).

<sup>b</sup> Reflex/confirmation dependent on regulatory requirements and/or testing availability.

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## Appendix 5. World Health Organization Classification for Diabetes

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**Type 1 Diabetes Mellitus:** T1DM is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia, but also to prevent spontaneous ketosis and death (Bennett 1991; Alberti and Zimmet 1998).

**Type 2 Diabetes Mellitus:** T2DM, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, and weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in T2D, but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) because of acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with T2D later progress to a state of absolute insulin deficiency (Bennett 1991; Alberti and Zimmet 1998).

## **Appendix 6. Classification of Contraceptive Methods**

Women of child-bearing 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. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). 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**

<b>Highly Effective Methods of Contraception</b>	<b>Effective Methods of Contraception (must use combination of 2 methods)</b>
<ul style="list-style-type: none"> <li>• Combined oral contraceptive pill and mini-pill</li> <li>• NuvaRing®</li> <li>• Implantable contraceptives</li> <li>• Injectable contraceptives (such as Depo-Provera®)</li> <li>• Intrauterine device (such as Mirena® and ParaGard®)</li> <li>• Contraceptive patch – ONLY women &lt;198 lb or 90 kg</li> <li>• Total abstinence</li> <li>• Vasectomy</li> </ul>	<ul style="list-style-type: none"> <li>• Male condom with spermicide</li> <li>• Female condom with spermicide</li> <li>• Diaphragm with spermicide</li> <li>• Cervical sponge</li> <li>• Cervical cap with spermicide</li> </ul>

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## Appendix 7. New York Heart Association Cardiac Disease Classification

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### Functional Capacity

#### **Class I**

Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

#### **Class II**

Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

#### **Class III**

Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

#### **Class IV**

Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

www.americanheart.org. ©2011, American Heart Association, Inc. 1994 Revisions to Classification of Functional Capacity and Objective Assessment of Patients with Diseases of the Heart

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**Appendix 8. Protocol Amendment I8B-MC-ITSI (a)  
Summary  
A Prospective, Randomized, Double-Blind, Crossover  
Comparison Evaluating Compatibility and Safety of  
LY900014 and Insulin Lispro with an External  
Continuous Subcutaneous Insulin Infusion System in  
Adult Patients with Type 1 Diabetes (PRONTO-Pump)**

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### **Overview**

Protocol I8B-MC-ITSI, A Prospective, Randomized, Double-Blind, Crossover Comparison Evaluating Compatibility and Safety of LY900014 and Insulin Lispro with an External Continuous Subcutaneous Insulin Infusion System in Adult Patients with Type 1 Diabetes (PRONTO-Pump) has been amended. The new protocol is indicated by amendment (a) 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-ITSI Amendment (a)**

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
Synopsis	Updated to match amended sections in main protocol	For consistency
Section 2 Schedule of Activities	Added line for collecting bolus types, updates to footnotes for bolus types	FDA request
Section 3.1 Study Rationale	Text updates to match Primary Objective	For consistency
Table ITSI.2 Objectives and Endpoints	Updated Objective and Endpoints 1, 2 and 3. And added an Objective 16 to compare factors affecting insulin dosing in pumps	FDA request to change hyperglycemia threshold to > 250 mg/dL, include a time frame (1 hour) and assess infusion site changes due to pain
Section 5.1 Overall Design	Text updates to match objectives	For consistency
Section 6.1 Inclusion Criteria #13	Edit to make infusion set and reservoir change more clear	FDA specified language
Section 7.1.3 Method of Treatment Assignment	Edit to make more clear	For clarity
Section 9.1.1. Primary Assessments	Text updates to match primary objective	FDA Request
Section 9.1.2. Secondary Assessments	Text updates to match objectives	FDA Request
Section 9.1.4.1.1 Correction Boluses	Text updates for clarity	For clarity and emphasis
Section 9.1.4.1.2. Infusion Set Changes	Text updates to match objective changed 'failure' to 'issue'	Category name in protocol changed from "failure" to "issue" to avoid confusion with primary objective "failure" term.
Section 9.1.4.2. Troubleshooting Unexplained Hyperglycemia	Added more procedural language for study subjects to check pump, infusion sets, and how to check blood ketones,	Protocol language added to address FDA request for ketone testing
Section 9.1.4.4. Diabetes Education and Nutritional Counseling	Added text 'use bolus types appropriately'	Additional patient education point
Section 10.1. Sample Size Determination	Added text for infusion set failures and BG threshold to match primary objective; Removed power analysis to detect a 4.55-fold increase	FDA request
Section 10.2. Populations for Analyses	Added CGM population	For clarity

Section # and Name	Description of Change	Brief Rationale
Section 10.3.1. General Statistical Considerations	Added more description for safety analyses and hypoglycemia analyses; Added statement about multiplicity adjustment for treatment group comparisons Added analysis for MMRM (1)- variables measured at multiple visits and MMRM (2)- variables measured once for each randomization period	For clarity
Section 10.3.2.1. Patient Disposition	Replaced treatment period with Period I and Period II	For clarity
Section 10.3.3.1. Primary Analyses	Text updates to match updates made to primary objective	For consistency
Section 10.3.3.2. Secondary Analyses	Text updates to match updates to secondary objectives; Added additional analyses for the rate and incidence for a subset of infusion set failures defined in the primary objective	FDA request
Section 10.3.3.3. Tertiary/Exploratory Analyses	Added by-day analysis plan	FDA request for treprostinil exposure over 3 days

## Revised Protocol Sections

**Note:** Deletions have been identified by ~~strikethroughs~~.  
Additions have been identified by the use of underscore.

### Synopsis

#### Rationale:

A high BG level that is not responding to a correction bolus via insulin pump may indicate an infusion set occlusion or insulin pump ~~problem~~ malfunction.

The aim of this study is to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of ~~suspected~~ infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with BG >300-BG >250 mg/dL (46.7-13.9 mmol/L) that does not decrease >50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change.

#### Objective(s)/Endpoints:

Objectives	Endpoints
<b>Primary Objective</b>	
1. To compare LY900014 and insulin lispro with respect to the rate of <del>suspected</del> <u>infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose &gt;300-250 mg/dL (46.7-13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction insulin bolus delivered via the pump and that leads to an infusion set change</u>	1. Rate (events/patient/30 days) of <del>suspected</del> <u>infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) &gt;300-250mg/dL (46.7-13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change during the 6-week treatment period</u>
<b>Secondary Objectives</b>	
2. To compare LY900014 and insulin lispro with respect to the incidence of <del>suspected</del> <u>infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose &gt;300-250 mg/dL (46.7-13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction insulin bolus delivered via the pump and that leads to an infusion set change</u>	2. Incidence (percent of patients with at least 1 event) of <del>suspected</del> <u>infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) &gt;300-250mg/dL (46.7-13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change during the 6-week treatment period</u>

Objectives	Endpoints
<p><del>3.</del> To compare LY900014 and insulin lispro with respect to the rate and incidence of <del>any suspected premature infusion set occlusions defined as unexplained hyperglycemia that leads to an infusion set change</del> <u>changes</u></p>	<p><del>3.</del> Rate (events/patient/30 days) and incidence of <del>any premature infusion set changes by reason (infusion set kinked, came out or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusions defined as unexplained hyperglycemia that leads to an infusion set change-occlusion; other)</del> during the 6-week treatment period</p>
<p><del>4.</del> To compare LY900014 and insulin lispro with respect to the rate and incidence of premature infusion set changes</p>	<p><del>4.</del> Rate (events/patient/30 days) and incidence of premature infusion set changes by reason during the 6-week treatment period</p>
<p><del>4.</del> <del>5.</del> To compare LY900014 and insulin lispro with respect to the <u>days-time interval</u> until infusion set change</p>	<p><del>4.</del> <del>5.</del> <u>Days/Time interval</u> until infusion set change during the 6-week treatment period</p>
<p><del>5.</del> <del>6.</del> To compare LY900014 and insulin lispro with respect to total, basal, and bolus insulin dose</p>	<p><del>5.</del> <del>6.</del> Bolus/total insulin dose ratio at the end of the 6-week treatment period</p>
<p><del>6.</del> <del>7.</del> To compare LY900014 and insulin lispro with respect to the interstitial glucose reduction rate from hyperglycemia following a non-meal-related correction <del>insulin</del> bolus delivered via the pump</p>	<p><del>6.</del> <del>7.</del> Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction <del>insulin</del> bolus via the pump, from hyperglycemia (interstitial glucose &gt;180 mg/dL [10 mmol/L]), to recovery (interstitial glucose ≤180 mg/dL), from up to 6 weeks of CGM use</p>
<p><del>7.</del> <del>8.</del> To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events</p>	<p><del>7.</del> <del>8.</del> Rate (events/patient/100 years) of severe hypoglycemic events during the 6-week treatment period</p>

**Statistical Analysis:**

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

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

Baseline is defined as the last nonmissing measurement at or before the randomization visit (Visit 3), unless otherwise specified.

The primary objective of this study is to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of ~~suspected infusion set occlusions defined as failures that lead to premature infusion set changes~~, due to a pump occlusion alarm or due to unexplained hyperglycemia with ~~BG > 300~~ blood glucose (SMBG) > 250 mg/dL (16.7/13.9 mmol/L) that does not decrease by ~~> 50 mg/dL (2.8 mmol/L)~~ within 1 hour following a correction bolus delivered via the pump ~~and that leads to an infusion set change~~, during the 6-week treatment period.

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

1. pump occlusion must meet alarm(s), OR
2. unexplained hyperglycemia that meets the following conditions:
  - ~~Led to an infusion set change~~
    - Associated with a non-meal related correction bolus delivered via the pump at least 1 hour before the infusion set change
    - Most recent self-monitored blood glucose (SMBG) within 1 hour before the correction bolus ~~> 300~~ > 250 mg/dL (16.7/13.9 mmol/L)
    - At least 1 SMBG obtained following the correction bolus prior to the infusion set change
    - ~~No SMBG measured~~ Within 1 hour (+10 minutes) following the correction bolus ~~(the most recent SMBG prior to the infusion set change)~~ indicates does not indicate a ~~> 50 mg/dL (2.8 mmol/L) decrease in blood glucose~~

If more than 1 non-meal-related correction bolus is given ~~via pump before the infusion set change~~ for an unexplained hyperglycemia, only the first correction bolus time will be used to determine the 1 hour (+10 minutes) timeframe following the correction bolus.

The analyses of the primary objective will be conducted on the ~~safety population~~ Safety Population including data collected prior to permanent discontinuation of investigational product- (i.e. last dose) in each randomized treatment period (Period I and Period II) and excluding data (if any) that are collected while patients temporarily are off pump or off IP. Treatment group comparisons will be performed using Wilcoxon signed-rank test at the full significance level of 0.05, with patients who are dosed in both treatment periods. No multiplicity adjustments will be made for the analysis of secondary and exploratory objectives.

The incidence (percent of patients with at least 1 event) of ~~suspected infusion set occlusion~~ failure as defined in the primary objective, ~~suspected infusion set occlusions~~, premature infusion set changes by reason, and severe hypoglycemia will be analyzed using Prescott's exact test.

~~Similarly,~~ The Wilcoxon signed-rank test will be used to analyze the rate of ~~suspected infusion set occlusions~~, premature infusion set changes by reason, and severe hypoglycemia, as described above for the primary endpoint.

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

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

**References:**

Grizzle JE. The two period change-over design and its use in clinical trials. *Biometrics*. 1965;21:467-480.

Thrasher J, Surks H, Nowotny I, Rotthacuser B, Wernicke Panten K, Garg S. Assessment of the safety of SAR342434 and Humalog when administered through insulin pump pilot study [poster]. In: American Diabetes Association 77th Scientific Sessions; Jun 9-13, 2017; San Diego (CA). Poster nr 1042-P.

**Section 2 Schedule of Activities**

eCRF Visit Number	1	2	3	4	5a	6	7	8a	9	801	ED
Review pump data for use in clinical decision making and data entry of required fields into Inform <sup>r</sup>		X	X	X		X	X		X		
<u>Record in Inform total number of meal-related bolus doses given as Normal, Square Wave, and Dual Wave during the 7 days prior to visit</u>		X	X	X		X	X		X	X	X
<u>Record in Inform any blood ketone meter test results</u>			X	X		X	X		X		X
<u>Review/discuss blood ketone meter test results, if applicable</u>			X	X		X	X		X		X
Synchronize the times of pump, eCOA, glucometer, <u>ketone meter</u> , and CGM receiver at site during visit		X	X	X		X	X				

r Enter into Inform current pump basal rates, CRs, ISFs, and AIT from Device Settings Snapshot; total basal units and total bolus units for last 3 days prior to visit, and total number of Normal, Square Wave, and Dual Wave bolus doses given during the last 7 days prior to the visit from Daily Detail report.

**Section 3.1 Study Rationale**

A high BG that is not responding to a correction bolus via insulin pump may indicate an infusion set occlusion or insulin pump ~~problem~~ malfunction.

The aim of this study is to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of ~~suspected infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia >300/250 mg/dL (16.7/13.9 mmol/L) that does not decrease >50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change.~~

Table ITSI.2 Objectives and Endpoints

Objectives	Endpoints
<b>Primary Objective</b>	
<p>1. To compare LY900014 and insulin lispro with respect to the rate of <del>suspected infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose &gt;300/250 mg/dL (16.7/13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction insulin bolus delivered via the pump and that leads to an infusion set change</del></p>	<p>1. Rate (events/patient/30 days) of <del>suspected infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) &gt;300 mg/250mg/dL (16.7/13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change</del> during the 6-week treatment period</p>
<b>Secondary Objectives</b>	
<p>2. To compare LY900014 and insulin lispro with respect to the incidence of <del>suspected infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose &gt;300/250 mg/dL (16.7/13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction insulin bolus delivered via the pump and that leads to an infusion set change</del></p>	<p>2. Incidence (percent of patients with at least 1 event) of <del>suspected infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) &gt;300 mg/250mg/dL (16.7/13.9 mmol/L) that does not decrease by &gt;50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change</del> during the 6-week treatment period</p>
<p>3. To compare LY900014 and insulin lispro with respect to the rate and incidence of <del>any suspected premature infusion set occlusions defined as unexplained hyperglycemia that leads to an infusion set change changes</del></p>	<p>3. Rate (events/patient/30 days) and incidence of <del>any premature infusion set changes by reason (infusion set kinked, came out or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusions defined as unexplained hyperglycemia that leads to an infusion set change occlusion; other) during the 6-week treatment period</del></p>
<p>4. <del>To compare LY900014 and insulin lispro with respect to the rate and incidence of premature infusion set changes</del></p>	<p>4. <del>Rate (events/patient/30 days) and incidence of premature infusion set changes by reason during the 6-week treatment period</del></p>

Objectives	Endpoints
4. <del>5</del> -To compare LY900014 and insulin lispro with respect to the <del>days-time interval</del> until infusion set change	4. <del>5</del> -Days/Time interval until infusion set change during the 6-week treatment period
5. <del>6</del> -To compare LY900014 and insulin lispro with respect to total, basal, and bolus insulin dose	5. <del>6</del> -Bolus/total insulin dose ratio at the end of the 6-week treatment period
6. <del>7</del> -To compare LY900014 and insulin lispro with respect to the interstitial glucose reduction rate from hyperglycemia following a non-meal-related correction <del>insulin</del> -bolus delivered via the pump	6. <del>7</del> -Interstitial glucose reduction rate (glucose reduction [mg/dL and mmol/L] per minute) within 4 hours following a non-meal-related correction <del>insulin</del> -bolus via the pump, from hyperglycemia (interstitial glucose >180 mg/dL (10.0 mmol/L) to recovery (interstitial glucose ≤180 mg/dL), from up to 6 weeks of CGM use
7. <del>8</del> -To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	7. <del>8</del> -Rate (events/patient/100 years) of severe hypoglycemic events during the 6-week treatment period
<b>Tertiary/Exploratory Objectives</b>	
8. <del>9</del> -To compare the safety of LY900014 and insulin lispro	8. <del>9</del> -Adverse events and vital signs
9. <del>10</del> -To compare LY900014 and insulin lispro with respect to the rate and incidence of documented symptomatic post-meal hypoglycemia	9. <del>10</del> -Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic post-meal hypoglycemia within 1 and 2 hours after the start of a meal during the last 2 weeks of the 6-week treatment period
10. <del>11</del> -To compare LY900014 and insulin lispro with respect to the rate and incidence of documented symptomatic hypoglycemia	10. <del>11</del> -Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with events) of documented symptomatic hypoglycemic events during the last 2 weeks of the 6-week treatment period
11. <del>12</del> -To compare LY900014 and insulin lispro with respect to the incremental AUCs after breakfast, obtained from CGM use	11. <del>12</del> -Incremental AUC <sub>0-1 hour</sub> after breakfast during the last 2 weeks of up to 6 weeks of CGM use
12. <del>13</del> -To compare LY900014 and insulin lispro with respect to the duration of time glucose values are within target range (71 and 180 mg/dL [3.9 and 10.0 mmol/L]), obtained from CGM use	12. <del>13</del> -Duration (in minutes) and percentage of time with glucose values between 71 and 180 mg/dL (3.9 and 10.0 mmol/L), both inclusive, normalized to a 24-hour period, during the last 2 weeks of up to 6 weeks of CGM use
13. <del>14</del> -To compare LY900014 and insulin lispro with respect to the duration of time glucose values are within target range (71 and 140 mg/dL [3.9 and 7.8 mmol/L]), obtained from CGM use	13. <del>14</del> -Duration (in minutes) and percentage of time with glucose values between 71 and 140 mg/dL (3.9 and 7.8 mmol/L), both inclusive, normalized to a 24-hour period, during the last 2 weeks of up to 6 weeks of CGM use
14. <del>15</del> -To compare LY900014 and insulin lispro with respect to the glucose profiles, obtained from CGM use	14. <del>15</del> -Average glucose for a 24-hour period during the last 2 weeks of up to 6 weeks of CGM use
15. <del>16</del> -To compare LY900014 and insulin lispro with respect to the glucose variability, obtained from CGM use	15. <del>16</del> -Interquartile range, CV, LBGI, and HBGI during the last 2 weeks of up to 6 weeks of

Objectives	Endpoints
16. <u>To compare LY900014 and insulin lispro with respect to the factors affecting dosing in pumps</u>	CGM use 16. <u>Actual and change from baseline in factors affecting dosing in pump (breakfast CR, AIT, breakfast ISF, and frequency of use of non-normal bolus type [Square Wave or Dual Wave]), during the 6-week treatment period</u>

### Section 5.1 Overall Design

The study is designed to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of ~~suspected infusion set occlusions defined as failures that lead to premature infusion set changes due to a pump occlusion alarm OR due to unexplained hyperglycemia  $>300$  with blood glucose (SMBG)  $>250$  mg/dL (46.7/13.9 mmol/L) that does not decrease  $>50$  mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change.~~ The study includes a 1-week screening period and a 2-week lead-in period followed by a 2-period crossover and a 4-week post-treatment safety follow-up. Each period of the crossover will consist of 6 weeks of treatment with no washout between periods.

Unexplained hyperglycemia is expected to be an uncommon event in this study and the use of real-time CGM, self-monitored blood glucose (SMBG), electronic clinical outcomes assessment (eCOA), frequent study visits, and provision of standard of care hyperglycemia troubleshooting management guidelines and blood ketone testing meters and strips will all serve to maximize subject safety. Patients will be experienced pump users who have recent experience using CGM or flash glucose monitoring (FGM), and they will be guided to follow best standards of care in insulin pump management.

At every office visit, the date and time of each device used in the study (insulin pump, eCOA diary, glucometer, ketone meter, and CGM receiver) should be synchronized and verified by site staff.

### Section 6.1 Inclusion Criteria

[13] Are willing to ~~change both the pump reservoir and adhere to an infusion set and reservoir change interval of every  $72 \pm 4$  hours unless necessary to maintain glycemic control in the event of a pump or change is required for failure of the infusion set/site malfunction~~

### Section 7.1.3. Method of Treatment Assignment

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

Patients will fill a new pump reservoir and infusion set with IP, then insert a new pump infusion set cannula into an appropriate site, and begin infusion of IP prior to leaving the investigative site at Visits 2, 3, and 6. Patients will continue to fill reservoirs and infusion sets with IP and insert a new infusion set cannula into an appropriate site every  $72 \pm 4$  hours as outpatients, unless a change is required for failure of the infusion set

## Section 8.2. Discontinuation from the Study

- Frequent use of prohibited concomitant medication.

### Section 9.1.1. Primary Assessments

The rate of ~~suspected~~ infusion set occlusions is defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia  $>300$  with blood glucose (SMBG)  $>250$  mg/dL ( $16.7$ - $13.9$  mmol/L) that does not decrease  $>50$  mg/dL ( $2.8$  mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change.

### Section 9.1.2. Secondary Assessments

- The incidence of ~~suspected~~ infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia  $>300$  with blood glucose (SMBG)  $>250$  mg/dL ( $16.7$ - $13.9$  mmol/L) that does not decrease  $>50$  mg/dL ( $2.8$  mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change
- ~~Rate and incidence of any suspected infusion set occlusions defined as unexplained hyperglycemia that leads to an infusion set change~~
- Rate and incidence of premature infusion set changes by reason (~~non-routine infusion set changes~~) by reason (infusion set kinked, came out or leaking; empty pump reservoir; infusion site pain or redness; pump occlusion alarm; suspected infusion set occlusion; other)
- ~~Days~~ Time interval until infusion set change (overall and due to any suspected infusion set occlusion)
- Interstitial glucose reduction from hyperglycemia following a non-meal-related correction ~~insulin~~ bolus delivered via the pump

#### Section 9.1.4.1.1 Correction Boluses

Patients will be instructed to enter the date, time, and dose for all non-meal-related correction bolus doses (those not associated with a meal or combined with a meal bolus) into the eCOA diary. This information is critical data for evaluating the primary objective of the study.

#### Section 9.1.4.1.2. Infusion Set Changes

The eCOA system will be used by patients to collect all infusion set changes, including date and time of change, designation of routine or premature change, primary reason for premature

change (~~infusion set failure~~ [infusion set kinked, came out, or leaking]; empty pump reservoir infusion site ~~complication~~ [pain or redness]; pump occlusion alarm; suspected infusion set occlusion; ~~or other~~).

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

Any interruption of CSII will need to be documented in the eCRF. When patients resume use of pump following the interruption, the first infusion set insertion change that occurs should be entered as “routine” infusion set change in eCOA.

#### **Section 9.1.4.2. Troubleshooting Unexplained Hyperglycemia**

Investigators will review unexplained hyperglycemia troubleshooting and management with patients at Visit 2 and may repeat as necessary at subsequent visits. Troubleshooting guidelines for unexplained hyperglycemia management will be provided as a tool for patient use. A blood ketone meter and test strips will be provided to each patient to aid in hyperglycemia management. All episodes of unexplained hyperglycemia  $>250$  ~~to~~  $>300$ -mg/dL should be confirmed by SMBG using the study glucometer. Patients should check to ensure the pump is in place, the prior bolus dose was delivered, and the infusion set is in place without any leaks or kinks in the system. All non-meal-related correction boluses including date, time, and dose should be entered into eCOA. Glucose response to the correction bolus should be confirmed by SMBG ~~within~~ in approximately 1 hour. Blood ketones should be tested when unexplained hyperglycemia occurs with blood glucose  $>250$  mg/dL (13.9 mmol/L) or a pump occlusion alarm occurs with blood glucose  $>250$  mg/dL (13.9 mmol/L). If blood ketones are positive ( $>0.6$  mmol/L) or nausea and/or vomiting is present, the patient should inject the correction dose by syringe, change the insulin, reservoir, and infusion set, and continue to monitor BG every 1 to 2 hours until within range. If BG is not responding to correction, and/or signs of DKA are present, the patient should go immediately to the nearest emergency room.

#### **Section 9.1.4.4. Diabetes Education and Nutritional Counseling**

Initial training at Visit 2 will include diabetes education and nutrition counseling. Training will include a review of correct pump use (frequency of reservoir and infusion set changes, priming of the infusion set, infusion site rotation) and review patient’s ability to carb count, use the pump’s bolus calculator to determine bolus and correction doses, use bolus types appropriately, treat hypoglycemia, etc.

#### **Section 10.1. Sample Size Determination**

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

The primary objective of this study is to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of ~~suspected infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with BG >300~~ blood glucose (SMBG) >250 mg/dL (16.7/13.9 mmol/L) that does not decrease by >50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump ~~and that leads to an infusion set change during the 6-week treatment period.~~

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

~~Assuming the number of suspected infusion set occlusions defined in the primary objective follows a negative binomial distribution with a dispersion parameter of 0.29, and a rate of 0.44 events/patient/30 days for insulin lispro (derived based upon Thrasher et al. 2017), 42 completers (21 completers in each treatment sequence) will provide at least 80% power to demonstrate a 4.55 fold increase in the event rate (equal to a rate of 2 events/patient/30 days for LY900014), using Wilcoxon signed rank test with a 2 sided alpha level of 0.05. The power was calculated based on the proportion of the trials showing statistical significance from 5000 simulated trials.~~

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

## Section 10.2 Populations for Analyses

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

### Section 10.3.1. General Statistical Considerations

Safety analyses will be conducted on the ~~safety population and~~ Safety Population. Analyses of AEs (including DKA) will only include all data collected during the course of the entire 6-week treatment period for each treatment group regardless of IP use. Analyses of hypoglycemia will be conducted on data collected prior to permanent discontinuation of IP (Section 8.1). (i.e. last dose) of IP in each 6-week treatment period. Unless otherwise specified, pump-related safety analyses (infusion set failures, premature infusion set changes, time interval until infusion set change, and interstitial glucose reduction rate) will exclude data (if any) that are collected while patients temporarily are off pump or off IP. Data collected during the safety follow-up period will not be used for comparisons between treatment groups.

Exploratory efficacy analyses (e.g., 1,5 AG and HbA1c) will be conducted on all randomized patients according to the treatment the patients are assigned to, ~~using data collected prior to permanent discontinuation of IP.~~ and CGM analyses will be conducted on the CGM Population.

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

Treatment group comparisons will be performed for the primary objective (Section 10.3.3.1) at the full significance level of 0.05. No multiplicity adjustment will be made for secondary and exploratory objectives.

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

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

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

### **Section 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 overall and by treatment sequence and period. Reasons for discontinuation from the study during ~~the treatment period~~ Period I and Period II will be summarized by treatment sequence and period.

Reasons for discontinuation from the study during the lead-in and follow-up periods will be summarized for overall population.

### Section 10.3.3.1. Primary Analyses

The primary objective of this study is to compare LY900014 and insulin lispro with respect to the rate (events/patient/30 days) of suspected infusion set occlusions defined as failures that lead to premature infusion set changes, due to a pump occlusion alarm or due to unexplained hyperglycemia with ~~BG >300~~ blood glucose (SMBG) >250 mg/dL (16.7/13.9 mmol/L) that does not decrease by >50 mg/dL (2.8 mmol/L) within 1 hour following a correction bolus delivered via the pump and that leads to an infusion set change, during the 6-week treatment period.

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

1. pump occlusion must meet alarm(s), OR
2. unexplained hyperglycemia that meets the following conditions:
  - ~~Led to an infusion set change~~
    - Associated with a non-meal-related correction bolus delivered via the pump at least 1 hour before the infusion set change
    - Most recent SMBG self-monitored blood glucose (SMBG) within 1 hour before the correction bolus >300/250 mg/dL (16.7/13.9 mmol/L)
    - At least 1 SMBG obtained following the correction bolus prior to the infusion set change
    - ~~No SMBG measured~~ Within 1 hour (+10 minutes) following the correction bolus (the most recent SMBG prior to the infusion set change) indicates does not indicate a >50 mg/dL (2.8 mmol/L) decrease in blood glucose

If more than 1 non-meal-related correction bolus is given via pump before the infusion set change for an unexplained hyperglycemia, only the first correction bolus time will be used to determine the 1 hour (+10 minutes) timeframe following the correction bolus as described in Section 9.1.4.1.1.

The infusion set failure rate (events/patient/30 days) will be derived for each patient for the lead-in, Period I and Period II, and summarized by treatment sequence for all patients in the Safety Population.

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

### Section 10.3.3.2. Secondary Analyses

The incidence (percent of patients with at least 1 event) of ~~suspected~~ infusion set ~~occlusions~~failures, as defined in the primary objective, ~~any suspected infusion set occlusions~~, premature infusion set changes by reason, and severe hypoglycemia will be analyzed using Prescott's exact test.

Similarly, Wilcoxon signed-rank test will be used to analyze the rate of ~~suspected~~ infusion set ~~occlusions~~failures, premature infusion set changes by reason, and severe hypoglycemia, as described in Section 10.3.3.1.

As an additional analysis, the rate and incidence will be determined for infusion set failures leading to premature infusion set changes due to unexplained hyperglycemia with blood glucose >250mg/dL that does not decrease by >50mg/dL within 1 hour following a correction bolus delivered via the pump, and analyzed in the same way as described for the primary endpoint.

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

Other safety measures will include AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro. Analyses will be performed on data collected over the ~~126~~-week treatment period for each treatment group.

Both date and time of all infusion set changes will be captured and daytime interval until infusion set change will be derived through ~~an hours a minute-to-days~~hour conversion.

Actual and change from baseline in basal, bolus, and total dose, as well as the bolus/total insulin dose ratio, will be analyzed by ~~at~~the MMRM model as described in Section 10.3.1.

As described in Section 10.3.1, continuous safety variables (for example, time interval~~days~~ until infusion change), as well as the change from baseline for these variables (if applicable), will be analyzed by the MMRM ~~model~~models, and categorical variables will be analyzed using Prescott's exact test for treatment comparisons unless otherwise specified.

~~The analyses~~Details for assessing immunogenicity data will be described in the SAP. No statistical comparisons between treatment groups will be conducted for immunogenicity data because patients will be exposed to both LY900014 and insulin lispro due to the crossover design.

### Section 10.3.3.3. Tertiary/Exploratory Analyses

Continuous variables and the change from baseline for these variables will be analyzed by the MMRM ~~model~~models as described in Section 10.3.1. Categorical variables will be analyzed either by model (for example, a generalized linear mixed model) or nonparametric methods (for example, Wilcoxon signed-rank test or Prescott's exact test). ~~Analysis details for the tertiary endpoints will be described in the SAP.~~

To assess the glucose control over the course of approximately 72-hours of continuous infusion, the duration and percentage of time in ranges (target, hypoglycemia or hyperglycemia) and incremental AUCs after breakfast, will be derived based upon the CGM raw data collected on Day 1, Day 2 and Day 3 of infusion set catheter wear and summarized by treatment group.

Analysis details for the tertiary endpoints will be described in the SAP.