Protocol I8B-MC-ITSM (b)

Evaluation of LY900014 in a Medtronic Pump

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Evaluation of LY900014 in a Medtronic Pump

LY900014

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Table of Contents

Section **Page**

List of Tables

List of Figures

List of Appendices

1. Synopsis

Title of Study:
Evaluation of LY900014 in a Medtronic Pump.

Rationale:
The aim of this study is to compare LY900014 and Humalog with respect to the percentage of time with glucose values within range (70 to 180 mg/dL) when both are delivered via continuous subcutaneous insulin infusion (CSII) by the Medtronic MiniMed 670G System while in Auto Mode as much as possible.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
1. To compare LY900014 and Humalog with respect to the percentage of time with sensor glucose values within range (70 to 180 mg/dL)	1. Percentage of time with sensor glucose values between 70 and 180 mg/dL (both inclusive), during the last 2 weeks of each 4-week treatment period
Secondary	
2. To compare LY900014 with Humalog with respect to the mean sensor glucose	2. Mean sensor glucose value (mg/dL), during the last 2 weeks of each 4-week treatment period
3. To compare LY900014 and Humalog with respect to the percentage of time spent in Auto Mode	3. Percentage of time (per week) spent in Auto Mode, during the last 2 weeks of each 4-week treatment period
4. To compare LY900014 with Humalog with respect to the percentage of time with sensor glucose values in hypoglycemic glucose ranges	4. Percentage of time with sensor glucose values <54 mg/dL during the last 2 weeks of each 4-week treatment period
5. To compare LY900014 and Humalog with respect to the rate of severe hypoglycemic events	5. Rate (events/patient/100 years) of severe hypoglycemic events during each 4-week treatment period
6. To compare LY900014 and Humalog with respect to the rate and incidence of documented hypoglycemia	6. Rate (events/patient/year) and incidence (percent of patients with events) of documented hypoglycemic events, during the last 2 weeks of each 4-week treatment period
7. To compare LY900014 and Humalog with respect to total daily dose	7. Mean total daily bolus insulin dose and mean total daily basal insulin dose during the last 2 weeks of each 4-week treatment period

Summary of Study Design:

This study is a prospective, randomized, double-blind, outpatient, 2-treatment crossover, active-controlled study conducted in patients with type 1 diabetes mellitus (T1D) currently using an external CSII. In the 2 treatment periods, LY900014 and Humalog will be delivered via the Medtronic MiniMed 670G system while in Auto Mode as much as possible.

The study is designed to compare LY900014 and Humalog with respect to the duration of time glucose values are within range (70 to 180 mg/dL).

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, each period consisting of 4 weeks of treatment, and a 2-week post-treatment safety follow-up.

Following the lead-in period, a 3-day pilot safety assessment will be conducted at a single site for the first 10 patients randomized. This pilot safety assessment will determine if the control algorithm in the Medtronic 670G pump can be used safely in patients receiving LY900014.

Number of Patients:

Approximately 50 participants will be screened to achieve 42 randomized for a total of approximately 36 patients to complete the study.

Statistical Analysis:

Statistical analysis of this study will be the responsibility of Lilly or its designee. Additional exploratory analyses of data will be conducted, as deemed appropriate.

Unless otherwise specified, all efficacy and safety analyses will be conducted on the Randomized Population. Analyses of adverse events (AEs) will include all data collected during the course of the entire 4-week treatment period for each treatment regardless of investigational product (IP) use. Analyses of hypoglycemia will be conducted from first dose to last dose of IP in each 4-week treatment period. Data collected during the safety follow-up period will not be used for comparisons between treatments.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.10, and confidence intervals (CIs) will be calculated at 90%, 2-sided.

Treatment comparisons will be performed for the primary objective at the full significance level of 0.10. No multiplicity adjustments will be made for the analysis of secondary and exploratory objectives.

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

The primary objective of this study is to compare LY900014 and Humalog with respect to the percentage of time with sensor glucose (SG) values within range (70 to 180 mg/dL), during the

last 2 weeks of each 4-week treatment period. The analysis model and selection of covariance structure are described below.

Unless otherwise specified, a restricted maximum likelihood based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit during the 4-week treatment period for each treatment will be included in the analysis. The model will include the fixed-class effects of treatment, period, sequence, strata (hemoglobin A1c; HbA1c [≤7.0%, >7.0%] and percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization [≤75%, >75%]), and the continuous, fixed covariate of baseline value. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, a covariance structure of compound symmetry without heterogeneous variances will be used. If the model still does not converge, strata may be deleted from the model. Significance tests will be based on least squares means and Type III tests. SAS PROC MIXED will be used to perform the analysis.

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

2. Schedule of Activities

Table ITSM.1. Schedule of Activities

	Screening	Lead-In		Study Period I				Study Period II			Safety Follow-up	Early Termination
Visit	**1**	**2**	**3[a]**	**4**	**5[a]**	**6[a]**	**7**	**8[a]**	**9[a]**	**10**	**801**	**ET**
Week of Treatment	**-3**	**-2**	**-1**	**0**	*****	**2**	**4**	*****	**6**	**8**	**10**	
Visit Window (±days)	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	
Study Logistics												
Informed consent signed	X											
Eligibility Criteria Reviewed	X	X										
Randomization				X								
IWRS	X	X	X	X	X	X	X	X	X	X	X	X
Crossover							X					
Clinical Assessments												
Patient demographics	X											
Medical history and preexisting conditions	X											
Physical examination/height	X											
ECG (12-lead)[b]	X											
Body weight	X	X		X			X			X	X	X
Vital signs: blood pressure/pulse rate[c]	X	X		X			X			X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Patient Education and Management												
Set standardized high/low glucose alerts		X		X			X					
At screening, record pump bolus delivery speed (Standard [1.5 U/min] or Quick [15 U/min]). At other office visits, confirm and record pump bolus delivery speed unchanged from screening.	X	X		X			X			X		
At screening, record infusion set cannula length (6mm or 9mm). If changed during study, record infusion set cannula length (6mm or 9mm) and reason for change.	X	X		X			X			X		
Reset pump ISF, CR, and AIT to randomization settings							X					
Change infusion set and reservoir at investigative site[d]		X		X			X			X[e]		X[e]

	Screening	Lead-In		Study Period I				Study Period II			Safety Follow-up	Early Termination
Visit	**1**	**2**	**3[a]**	**4**	**5[a]**	**6[a]**	**7**	**8[a]**	**9[a]**	**10**	**801**	**ET**
Week of Treatment	**-3**	**-2**	**-1**	**0**	*****	**2**	**4**	*****	**6**	**8**	**10**	
Visit Window (±days)	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	
Review/Answer questions on Medtronic 670G System, Diabetes management education, carbohydrate counting, collecting 4-point SMBG profiles, and review hypoglycemia and hyperglycemia management guidelines[f,g]		X										
Review total daily insulin dose[h]	X											
Review pump, CGM, and SMBG data for use in clinical decision making		X	X	X	X	X	X	X	X	X		X
Review/discuss hypoglycemia data			X	X	X	X	X	X	X	X	X	X
Remind patient to upload pump data to CareLink weekly		X	X	X	X	X	X	X	X	X		
Ancillary Supplies/Diaries/IP												
Dispense infusion sets, reservoirs, BG test strips, and ancillary supplies		X		X			X			X	X	
Dispense Study Diary		X		X			X			X		
Collect Study Diary and review with patient				X			X			X	X	X
Start open-label Humalog at office visit		X										
Start non-study rapid-acting analog insulin at office visit										X		
Dispense IP				X			X					
Collect used and unused study drug and supplies from patient				X			X			X		X
Transfer Diary Data to eCRF												
Hypoglycemia events		X		X			X			X	X	X
Unplanned infusion set changes with noted reason(s)				X			X			X	X	X
Transfer CareLink Data to eCRF												
Pump settings: ISF, CR, AIT (used to start next treatment)		X		X			X					
Mean total daily bolus and basal insulin dose[i]		X		X			X			X		X
Time in Auto Mode per week (%)[i]		X		X			X			X		X
Laboratory Assessments												
Follicle-stimulating hormone test[j]	X											
Serum pregnancy test	X											
Urine pregnancy test				X								

	Screening	Lead-In		Study Period I				Study Period II			Safety Follow-up	Early Termination
Visit	**1**	**2**	**3[a]**	**4**	**5[a]**	**6[a]**	**7**	**8[a]**	**9[a]**	**10**	**801**	**ET**
Week of Treatment	**-3**	**-2**	**-1**	**0**	*****	**2**	**4**	*****	**6**	**8**	**10**	
Visit Window (±days)	**0**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	
Chemistry panel	X											
Urinalysis panel	X											
Hematology	X											
1.5-Anhydroglucitol				X			X			X		X
Hemoglobin A1c	X			X			X			X		X
Pilot Safety Assessment Specific[k]												
Instruct designated study companion on their responsibilities throughout the pilot safety assessment and ensure familiarity with basic features of the MiniMed 670G pump[l]				X								
Ensure patient upload of CareLink Data is completed for review					X							
Transfer patient diary data entries related to hypoglycemia, unexplained hyperglycemia and unplanned infusion set changes into eCRF. Review and discuss all patient diary entries.					X							

Abbreviations: AIT = active insulin time; BG = blood glucose, CGM = continuous glucose monitoring; CR = carb ratio; ECG = electrocardiogram; ET = early termination; IP = investigational product; ISF = insulin sensitivity factor; IWRS = interactive web-response system; SMBG = self-monitored blood glucose.

* Denotes 3-day safety follow-up telephone visit after the beginning of each study period.

a Telephone visits are indicated by columns shaded a darker shade of gray.

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

c 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.

d All study procedures for a visit should be completed prior to reservoir and infusion set changes during Visits 2, 4, 7, 10 and 801 or ET.

e At Visit 10 or ET, patients should resume nonstudy insulin. Patients should be instructed to bring their nonstudy insulin with them to the visit in order to resume normal therapy.

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

g Patients should be instructed to perform, at minimum, a 4-point SMBG profile daily starting at Visit 2.

h From each of the last 3 days prior to screening

i Mean from the 1 week prior to Visit 2; mean from the 2 weeks prior to visit for Visits 4, 7, 10, and ET.

j 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.

k Patients participating in the pilot safety assessment will complete all activities listed in the schedule of activities in addition to all pilot-specific activities. These activities do not need to be completed for patients not participating in the pilot safety assessment.

l Designated study companions must be present to receive instruction at Visit 4.

3. Introduction

3.1. Study Rationale

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

An ultra-rapid-acting prandial insulin that would shift the pharmacokinetic (PK) and pharmacodynamic (PD) 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 (T1D) and type 2 diabetes mellitus (T2D) when delivered by multiple daily injections (MDI), continuous subcutaneous insulin infusion (CSII), or in closed loop and hybrid closed loop automated insulin delivery systems.

The performance of closed loop and hybrid closed loop insulin delivery systems is limited by the relatively slow absorption of current rapid-acting insulin analogs, delaying the onset of action and prolonging the duration of action. This is problematic during times of rapid glucose changes, such as in the postprandial period. It is hypothesized that rapid glucose changes will be minimized with an ultra-rapid-acting insulin in a hybrid closed loop system. The integration of an ultra-rapid insulin with an accelerated PK profile into a hybrid closed loop algorithm may increase time patients spend in the target glucose range.

The aim of this study is to compare LY900014 and Humalog with respect to the percentage of time with glucose values within range (70 to 180 mg/dL) when both are delivered via CSII by the Medtronic MiniMed 670G System while in Auto Mode as much as possible.

3.2. Background

There have been many advances in the treatment of T1D in the last 20 years; however, reaching goals and maintaining glycemic targets remain 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). Integrated insulin pump and continuous glucose monitoring (CGM) systems may provide better diabetes management, compared with MDI or with the pump alone. Some studies suggest that when you pair pump therapy with the information provided by a glucose sensor, it may significantly improve HbA1c levels without increasing the risk of hypoglycemia (Bergenstal et al. 2010, Battelino et al. 2012, Bergenstal et al. 2013).

LY900014

LY900014 is comprised of the active ingredient, insulin lispro, and 2 enabling excipients (treprostinil and citrate) that facilitate rapid absorption of insulin lispro into the blood stream. This novel formulation results in earlier glucose lowering when compared with Humalog. This

faster glucose-lowering response, as demonstrated by the PK and PD profiles of LY900014 when compared with Humalog, more closely mimics the time-action profile of normal endogenous insulin secretion. This enhanced activity is expected to provide greater glycemic control as dosing relative to the start of a meal can be reduced when compared with the timing required for the currently available rapid-acting insulin analogs. Dosing closer to the start of a meal will allow patients to better match the needed insulin dose to the carbohydrate content of their meal.

Medtronic MiniMed 670G System

The Medtronic MiniMed 670G system is intended for continuous delivery of basal insulin and administration of insulin boluses for the management of T1D and for the continuous monitoring of interstitial glucose levels. The Medtronic MiniMed 670G System consists of the MiniMed 670G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), and the CONTOUR NEXT Link 2.4 Glucose Meter. The Guardian Sensor (3) is intended to be used for detecting sensor glucose (SG) trends and tracking patterns and to be used by the MiniMed 670G system to automatically adjust basal insulin levels. It is indicated for use as an adjunctive device to compliment, but not replace standard blood glucose (BG) testing.

The MiniMed 670G System includes SmartGuard technology. There are 2 levels of SmartGuard technology; Suspend and Auto Mode.

The first level of SmartGuard technology automatically suspends insulin when the sensor reaches a preset low limit (*Suspend on low*) or before the low limit is reached (*Suspend before low*). When a *Suspend before low* occurs, insulin delivery will automatically resume when the SG levels recover. The *Suspend on low* and *Suspend before low* features are optional features available only when the system is in Manual Mode.

Study I8B-MC-ITSM (ITSM) will use the second level of SmartGuard technology, Auto Mode, as much as possible. Auto Mode automatically calculates insulin dose using Guardian Sensor (3) data. Auto Mode is an insulin delivery feature that automatically controls basal insulin delivery to regulate glucose levels to a target SG. The standard target SG setting is 120 mg/dL and the target can be set temporarily to 150 mg/dL for exercise and other events. During Auto Mode operation, the user must deliver meal boluses. The Bolus feature in Auto Mode requires entry of either carbohydrate or a BG value, but both may be entered. Auto Mode then calculates the bolus amount needed to cover the meal or correction. Auto Mode Bolus only allows *Normal* boluses. *Square Wave*, *Dual Wave*, *Easy*, *Manual*, *Remote*, and *Preset* bolus types cannot be delivered while in Auto Mode.

Basic requirements for managing Auto Mode include the following:

- Periodic BG testing to calibrate the sensor. Minimum calibration is every 12 hours.
- Use of Auto Mode Bolus function to cover meals, and when the pump recommends a bolus. A BG reading above 150 mg/dL causes Auto Mode to automatically calculate if a correction bolus is needed to decrease BG to the 150 mg/dL correction target.

Safe Basal is an automatic function within Auto Mode. Safe Basal allows for time to perform additional actions required to ensure Auto Mode remains active. Safe Basal covers basal needs

by delivering insulin at a constant rate and does not adjust insulin delivery based on SG values. Several conditions can cause a transition into Safe Basal:

- Auto Mode has been at the minimum delivery limit for 2.5 hours.
- Auto Mode has been at the maximum delivery limit for 4 hours.
- Auto Mode detects that sensor might be under reading.
- An entered BG is 35% or more different than your current SG value.
- No SG data have been received for more than 5 minutes.

After 90 minutes in Safe Basal, if the condition that caused the pump to transition into Safe Basal has not been resolved, the pump will enter Manual Mode. The pump will indicate the actions the user needs to take to resume Auto Mode delivery of basal insulin.

Manual Mode refers to system functions other than Auto Mode. If Auto Mode is not functioning, the system is in Manual Mode.

3.3. Benefit/Risk Assessment

Across Phase 1 clinical studies, LY900014 has consistently demonstrated a faster time-action profile than Humalog. In patients with T1D or T2D treated with MDI insulin therapy, LY900014 significantly reduced postprandial glucose excursions compared with Humalog when both were dosed by syringe at the start of a test meal. Two studies (I8B-MC-ITRF and I8B-MC-ITSC) in patients with T1D 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.

Benefits to patients may include improved understanding of insulin requirements and optimization of pump settings in a hybrid closed loop system with a faster acting insulin. Additionally, close monitoring, frequent visits, real-time CGM and self-monitored blood glucose (SMBG) all serve to protect subject safety and minimize risk.

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 Humalog.

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. Diabetic ketoacidosis develops when insulin levels are insufficient to meet the body's basic metabolic requirements. Diabetic ketoacidosis is an acute metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. Signs and symptoms may include vomiting, abdominal pain, deep gasping breathing, increased urination, weakness, confusion, and occasionally loss of consciousness. A high BG that is not responding to a correction bolus via insulin pump may indicate an infusion set occlusion or insulin pump problem.

Following the lead-in period, a 3-day pilot safety assessment will be conducted at a single site for the first 10 patients randomized. This pilot safety assessment will determine if the control algorithm in the Medtronic 670G pump can be used safely in patients receiving LY900014.

Safety evaluation in this study will include hypoglycemia, treatment-emergent AEs (TEAEs), serious AEs (SAEs), clinical laboratory assessments, vital signs, pump occlusion alarms, and unexplained hyperglycemia leading to unplanned infusion set changes. More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY900014 can be found in the Investigator's Brochure (IB).

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

4. Objectives and Endpoints

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

Table ITSM.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
1. To compare LY900014 and Humalog with respect to the percentage of time with sensor glucose values within range (70 to 180 mg/dL)	1. Percentage of time with sensor glucose values between 70 and 180 mg/dL (both inclusive), during the last 2 weeks of each 4-week treatment period
Secondary	
2. To compare LY900014 with Humalog with respect to the mean sensor glucose	2. Mean sensor glucose value (mg/dL), during the last 2 weeks of each 4-week treatment period
3. To compare LY900014 and Humalog with respect to the percentage of time spent in Auto Mode	3. Percentage of time (per week) spent in Auto Mode, during the last 2 weeks of each 4-week treatment period
4. To compare LY900014 with Humalog with respect to the percentage of time with sensor glucose values in hypoglycemic glucose ranges	4. Percentage of time with sensor glucose values <54 mg/dL during the last 2 weeks of each 4-week treatment period
5. To compare LY900014 and Humalog with respect to the rate of severe hypoglycemic events	5. Rate (events/patient/100 years) of severe hypoglycemic events during each 4-week treatment period
6. To compare LY900014 and Humalog with respect to the rate and incidence of documented hypoglycemia	6. Rate (events/patient/year) and incidence (percent of patients with events) of documented hypoglycemic events, during the last 2 weeks of each 4-week treatment period
7. To compare LY900014 and Humalog with respect to total daily dose	7. Mean total daily bolus insulin dose and mean total daily basal insulin dose during the last 2 weeks of each 4-week treatment period
Tertiary/Exploratory	
8. To compare the safety of LY900014 and Humalog	8. Adverse events and vital signs
9. To compare LY900014 and Humalog with respect to the percentage of time with sensor glucose values within range (70 and 140 mg/dL)	9. Percentage of time with sensor glucose values between 70 and 140 mg/dL (both inclusive), during the last 2 weeks of each 4-week treatment period
10. To compare LY900014 and Humalog with respect to the rate and incidence of unplanned infusion set changes	10. Rate (events/patient/30 days) and incidence of unplanned infusion set changes by reason (Pump occlusion alarm, unexplained high BG, Infusion site reaction [pain, redness or swelling at infusion site], or Infusion set problem [infusion set kinked, pulled out, leaking, reservoir empty, etc]), during the 4-week treatment period
11. To compare LY900014 and Humalog with respect to the percentage of time with sensor glucose values in hyperglycemic glucose ranges	11. Percentage of time with sensor glucose values >180 mg/dL and >250 mg/dL, during the last 2 weeks of each 4-week treatment period

Objectives	Endpoints
12. To compare LY900014 and Humalog with respect to the 1-hour postprandial sensor glucose excursions	12. Mean 1-hour postprandial sensor glucose excursions (mean sensor glucose measured 1 hour after the start of the meal minus mean sensor glucose at the start of meal) after breakfast, during the last 2 weeks of each 4-week treatment period
13. To compare LY900014 and Humalog with respect to the within-patient sensor glucose variability	13. Coefficient of variation (CV) (standard deviation/mean) of sensor glucose values, during the last 2 weeks of each 4-week treatment period
14. To evaluate HbA1c of LY900014 and Humalog	14. Summary statistics of actual and change of HbA1c during each 4 week treatment period
15. To evaluate 1,5-AG of LY900014 and Humalog	15. Summary statistics of actual and change of 1,5-AG during each 4-week treatment period
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), during the 4-week treatment period

Abbreviations: 1,5 AG = 1,5 Anhydroglucitol; AIT = active insulin time; BG = blood glucose; CR = carb ratio; ISF = insulin sensitivity factor.

5. Study Design

5.1. Overall Design

This study is a prospective, randomized, double-blind, outpatient, 2-treatment , crossover, active-controlled study conducted in patients with T1D currently using an external CSII pump. In the 2 treatment periods, LY900014 and Humalog will be delivered via the Medtronic MiniMed 670G system with SmartGuard™ technology using AutoMode. In this study, patients will be required to use the Auto Mode insulin delivery function as much as possible.

The study is designed to compare LY900014 and Humalog with respect to the duration of time glucose values are within range (70 to 180 mg/dL). The study includes a 1-week screening period and a 2-week lead-in period followed by a 2-period crossover, each period consisting of 4 weeks of treatment, and a 2-week post-treatment safety follow-up.

Following the lead-in period, a 3-day pilot safety assessment will be conducted at a single site in the first 10 patients randomized. This pilot safety assessment will determine if the control algorithm in the Medtronic 670G pump can be used safely in patients receiving LY900014. Patients randomized into the pilot safety assessment will remain blinded to treatment and undergo study procedures in the Schedule of Activities with additions denoted at the bottom. These patients will be required to have additional safety oversight in the form of a designated study companion (spouse, a partner, or someone living in the household) who is required to be with the patient overnight for the first 3 days of the study. The investigative site will check in with the patient at Day 1 via a telephone call. During the Visit 5 telephone call, the investigator will review patient data and determine if the patient can continue study treatment. More details on the pilot safety assessment are described in Section 9.4.6.1.

The pilot patients will contribute to the total number of patients randomized. No additional patients will be randomized until after a blinded review of the pilot patients' safety data occurs. Within 1 week of all 10 patients completing the 3-day pilot safety assessment, the investigator will review the data in consultation with the Sponsor. After completion of the pilot safety assessment, the investigator and the Sponsor will determine if randomization can continue.

Study governance considerations are described in detail in Appendix 3.

Figure ITSM.1 illustrates the study design.

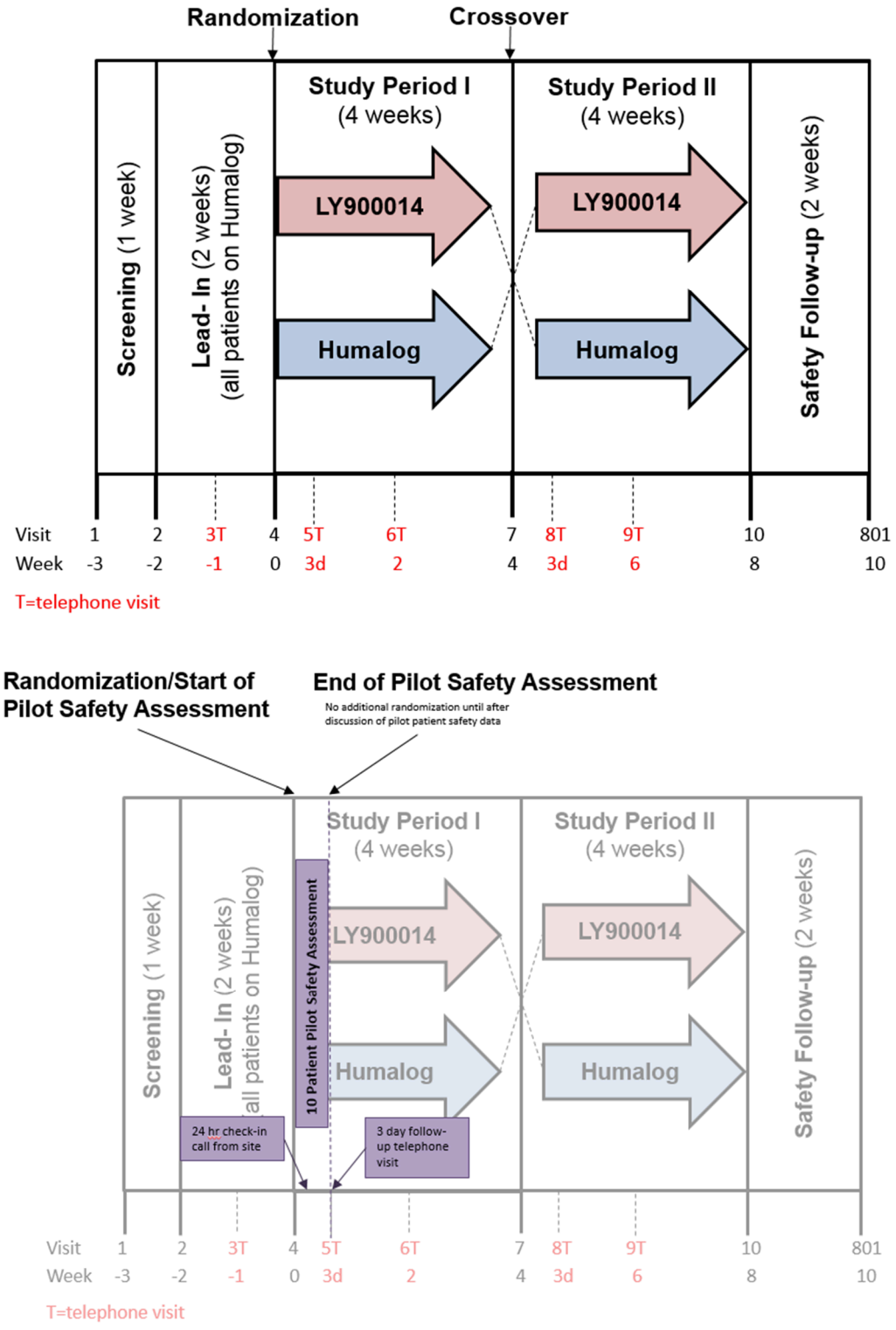

Figure ITSM.1. Illustration of study design for Clinical Protocol I8B-MC-ITSM.

5.2. Number of Participants

Approximately 50 participants will be screened to achieve 42 randomized for a total of approximately 36 patients to complete the study. Pilot patients will contribute to the overall number of participants.

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 pilot safety assessment was added to the study design after consultation with FDA in December 2018. The purpose of the pilot will be to assess the safety of LY900014 when administered via the Medtronic 670G pump before enrolling a large number of patients.

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. The investigator will reset the patient's pump to randomization settings. Treatment comparisons will use the data collected during the last 2 weeks of each period. This will minimize carryover effect on the primary analysis of efficacy, safety, and exploratory outcomes.

5.5. Justification for Dose

The basal and bolus delivery of insulin in this study will be determined based on the individual needs of each patient. LY900014 has the same insulin lispro concentration (100 U/mL) as that of commercially available Humalog. In Phase 3 clinical studies, LY900014 and Humalog were substituted unit for unit. Humalog has been in the market for over 20 years with widespread use worldwide and has extensive efficacy and safety data. 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 post dose) are similar between LY900014 and Humalog in T1D CSII. In addition, the total glucodynamic activity measured in euglycemic clamp studies was similar between LY900014 and Humalog.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted. There are additional criteria for patients who participate in the pilot safety assessment of the study.

6.1. Inclusion Criteria

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

Type of Patient and Disease Characteristics

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

Patient Characteristics

[2] Are at least 18 years of age

[3] Male patients:

a) No male contraception required.

[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 who are 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 5)

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

[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 or insulin aspart) via CSII for at least the last 30 days prior to screening

[7] Have HbA1c values ≥6.0 and ≤8.0%, as determined by the central laboratory at screening (Visit 1)

[8] Have a body mass index of ≤35 kg/m^2 at screening (Visit 1)

[9] Are proficient, in the opinion of the investigator, in carbohydrate counting

[10] Are willing to adhere to an infusion set and reservoir change interval of every 3 days.

[11] Must be using a Medtronic MiniMed 670G insulin pump

a) For at least 90 days prior to screening in Auto Mode

b) In Auto Mode at least an average of 70% of the time per week during the last 4 weeks prior to screening

c) With a Medtronic Guardian (3) sensor at least an average of 75% of the time per week during the last 4 weeks prior to screening

d) And willing to stay on the 670G pump throughout the study

e) And willing to maintain the bolus delivery speed used at screening for the duration of the study

f) And willing to avoid use of all products containing acetaminophen while using the Medtronic Guardian (3) sensor

g) And willing to use study-provided Medtronic MiniMed insulin pump reservoirs and Mio infusion sets

h) And willing to use the Auto Mode Bolus feature to deliver boluses to cover meals and corrections, and whenever the pump recommends a bolus

[12] Are willing to perform BG testing using their personal Contour Next Link 2.4 meter 4 times each day premeal and bedtime, including for sensor calibrations, and to confirm hypoglycemia and unexplained hyperglycemia, and willing to respond to periodic requests from the pump for BG readings without the need for calibration

[13] Have access to a telephone, or alternative means for close monitoring and communications

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

Informed Consent

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

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening or at other visits, only when indicated:

Medical Conditions

[16] Have hypoglycemia unawareness as judged by the investigator

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

[18] Have had any emergency department visit or hospitalization due to poor BG control (hyperglycemia or DKA) within 6 months prior to screening

[19] Have a total daily insulin dose >100 units, as determined by the average total daily insulin dose over the 3 days prior to screening.

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

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

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

[23] 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

[24] 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

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

[26] Renal:

a) History of renal transplantation

b) Currently receiving renal dialysis

c) Serum creatinine >2.0 mg/dL (177 μmol/L) at screening (Visit 1) as measured by the central laboratory

[27] Hepatic:

a) 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)

b) Total bilirubin level (TBL) ≥2X the upper limit of normal (ULN) (with the exception of Gilbert's disease) as defined by the central laboratory

Or

c) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3X ULN as defined by the central laboratory

[28] 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

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

[30] 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

[31] Have used insulin human inhalation powder (Afrezza®) within 2 weeks prior to screening

[32] Are receiving any oral or injectable medication intended for the treatment of diabetes other than rapid-acting analog insulin via CSII in the 30 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.

[33] Glucocorticoid therapy: are receiving chronic (lasting longer than 7 consecutive days) systemic glucocorticoid therapy (including intravenous, IM, subcutaneous, and oral), but excluding topical, intraocular, intranasal, intra-articular, and inhaled preparations), or have received such therapy within 2 weeks immediately prior to screening with the exception of replacement therapy for adrenal insufficiency

Prior/Concurrent Clinical Trial Experience

[34] Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study

[35] Have participated, within the last 30 days in a clinical study involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed;

Other Exclusions

[36] 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

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

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

[39] 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

Pilot Patients

[40] All patients participating in the pilot safety assessment must have an adult (≥18 years old) designated study companion that will reside at the same location overnight during the pilot and agree to sleep in the same room with the patient, sleep within hearing distance of the CGM and pump alarms, be willing to awaken at least once between 2:00 AM and 4:00 AM to assist the patient in checking BG, and be willing to assist the patient in troubleshooting an alarm if one should occur during the night. The designated study companion must agree to these responsibilities for the 3-day duration of the pilot safety assessment.

6.3. Lifestyle Restrictions

During the study, patients must avoid:

- donating blood or blood products
- major changes in diet or exercise
- all medications that contain acetaminophen.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, with the exception of individuals who screen fail due to;

- Inclusion

  [11] Must be using a Medtronic MiniMed 670G insulin pump

  b) In Auto Mode at least an average of 70% of the time per week during the last 4 weeks prior to screening

  c) With a Medtronic Guardian (3) sensor at least an average of 75% of the time per week during the last 4 weeks prior to screening

- Exclusion

  [19] Have a total daily insulin dose >100 units, as determined by the average total daily insulin dose over the 3 days prior to screening.

- Or Combination of any above

If an individual screen fails due to one of the reasons listed, the individual may be rescreened once, no sooner than 2 weeks after the initial screening. Patients who rescreen are not eligible to participate in the pilot safety assessment.

Retests, outside of rescreening, are not allowed, except for cases when results are not available from the original sample. It is expected that any lab or procedure performed in the initial screening be repeated for rescreened patients.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY900014 and Humalog delivered via CSII using the Medtronic MiniMed 670G insulin pump. Throughout the study, patients will use their personal Medtronic MiniMed 670G pump and the study provided, Guardian Link (3) Transmitter, Guardian Sensor (3) glucose sensors, and Contour Next Link 2.4 Blood Glucose Meter. Patients will be required to use the reservoirs and infusion sets provided by the investigative site. Table ITSM.3 shows the treatment regimens.

All patients not currently using insulin lispro in their pumps will begin using Humalog at the beginning of the 2-week lead-in period. Following the lead-in period, 10 patients will be randomized in a double-blind manner to 1 of the 2 treatment sequences in a 1:1 ratio and enter a pilot safety assessment. After completetion of the pilot safety assessment, the investigator along with Lilly will determine if randomization can continue.

Table ITSM.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 meal; correction bolus as needed; and basal infusion;
Humalog	100 U/mL	Individualized dosing	CSII	Mealtime bolus 0-2 min prior to start of meal; correction bolus as needed; and basal infusion

Abbreviations: CSII = continuous subcutaneous insulin infusion.

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

- Explaining the correct use of IP to the patient
- Explaining storage requirements for IP to the patient
- Maintaining accurate records of IP dispensing and collection
- At the end of the study, returning all used and unused IP to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labeling

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

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

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

7.1.2. Insulin Pumps

Patients will use their personal Medtronic MiniMed 670G pump, the study provided Contour Next Link 2.4 meter, and Medtronic Guardian Sensor (3) Transmitter and sensors throughout the study. All patients will be required to use MiniMed reservoirs and Mio infusion sets with 6-mm or 9-mm cannula and 32-inch tubing. If the infusion set cannula length is changed during the study, it should be documented. The Mio infusion set was chosen because of its all-in-one design that combines the infusion set with the inserter device.

7.1.2.1. Pump Bolus Delivery Speed

Patients will be allowed to use Standard (1.5 U/min) or Quick (15 U/min) pump bolus delivery speed. Patients must maintain the same speed throughout the entire study.

7.1.2.2. Pump Bolus Delivery Time

Patients will deliver bolus doses to cover carbohydrate intake at 0 to 2 minutes prior to consumption.

7.1.2.3. Pump Alerts

Patients should use the Auto Mode feature of their MiniMed 670G pump as much as possible throughout the trial, including use of the Auto Mode Bolus feature to deliver boluses to cover meals, and whenever the pump recommends a bolus.

Factory set Auto Mode Exit High and Low Sensor Glucose Alerts cannot be silenced and are always enabled when the pump is in Auto Mode.

The pump will exit Auto Mode based on a set SG threshold:

- 300 mg/dL or higher for 1 hour
- 250 mg/dL or higher for 3 hours
- 50 mg/dL or lower for any period of time.

Factory set Low Alert cannot be silenced and is always enabled, whether the pump is in Auto Mode or Manual Mode.

In addition, study site programmed Sensor Glucose Alerts will be standardized for all patients throughout the study. High Alerts will be set to occur when SG reaches >180 mg/dL and Low Alerts will be set to occur when SG reaches <70 mg/dL.

7.2. 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 4. 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 → Humalog
Sequence B: Humalog → LY900014

Stratification will be by HbA1c stratum (≤7.0%, >7.0% at Visit 1) and percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization (≤75%, >75%).

Patients will begin using a new reservoir and infusion set prior to leaving the investigative site at Visits 2, 4, 7 and 10. Patients will change the pump reservoir and infusion set every 3 days unless a change is required due to a failure of the infusion set.

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

7.3. Blinding

This is a double-blind study in which the treatments, LY900014 and Humalog, will have basal and bolus doses delivered 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.

7.4. Dosage Modification

See Section 7.1.2

7.5. Preparation/Handling/Storage/Accountability

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

- Confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- Ensuring that only participants enrolled in the study may receive IP and only authorized site staff may supply or administer study treatment.
- Ensuring all study treatments must be stored in a secure, 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, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

The investigator or designee will assess compliance of the patient at each visit, based on a review of the patient's CareLink reports, glycemic control, adherence to the visit and treatment schedule, and completion of the patient's study diary. Patients who are deemed noncompliant will receive additional diabetes education and training, as required, and the importance of compliance with the protocol will be reinforced. Patients who, in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from the study. No specific study data will be collected to analyze treatment compliance.

7.7. Concomitant Therapy

The following concomitant medications

- are NOT allowed at any time during the study;
    - Afrezza® (inhaled insulin)
    - Any noninsulin diabetes treatment therapy
    - Acetaminophen
    - Systemic glucocorticosteroid
        - IV, IM, SC, oral
            - except in the case of replacement therapy for adrenal insufficiency
- ARE allowed for a maximum of 48 hours during each treatment period
    - Basal insulin

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

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

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

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

7.8.2. Special Treatment Considerations

After discontinuation of IP at the end of the treatment period or earlier, randomized patients should start a nonstudy 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. If the investigator and the sponsor CRP/CRS agree that 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 other than the Medtronic MiniMed 670G.
- The patient has not used IP for more than 3 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
- A patient experiences any episode of clinically diagnosed Diabetic Ketoacidosis (DKA) during the study
    - DKA is defined as an acute metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. Hyperglycemia causes an osmotic diuresis with significant fluid and electrolyte loss. DKA causes nausea, vomiting, and abdominal pain and can progress to cerebral

edema, coma, and death. DKA is diagnosed by detection of hyperketonemia and anion gap metabolic acidosis in the presence of hyperglycemia. Treatment involves volume expansion, insulin replacement, and prevention of hypokalemia

- A patient participating in the pilot experiences any episode of severe hypoglycemia during the first 3 days of the pilot safety assessment
- A patient experiences >1 episode of severe hypoglycemia during the study
- A pilot patient's designated study companion does not comply with assigned responsibilities or is no longer available during pilot and transfer of study companion responsibilities is not possible for remainder of pilot safety assessment
- 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. Efficacy Assessments

9.1.1. Primary Assessments

Percentage of time in range (%) of target SG values collected.

9.1.2. Secondary Assessments

- Percentage of time in range (%) of hypoglycemic SG values collected
- Percentage of time (%) per week spent in Auto Mode
- Mean SG value
- Rate and incidence of hypoglycemia events
- Mean total daily basal insulin dose
- Mean total daily bolus insulin dose

9.1.3. Appropriateness of Assessments

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

9.1.4. Study Procedures

9.1.4.1. Continuous Glucose Monitoring

The Medtronic MiniMed 670G System consists of the following devices:

- MiniMed 670G Insulin Pump,
- Guardian Link (3) Transmitter,
- Guardian Sensor (3),
- CONTOUR NEXT Link 2.4 Glucose Meter.

Patients will use all of the System components throughout the trial. All therapy adjustments should be based on measurements obtained using the CONTOUR NEXT Link 2.4 Glucose Meter and not on values provided by the Guardian Sensor (3). The Guardian Sensor (3) is intended for use with the Medtronic MiniMed 670G system to continuously monitor glucose levels in patients with diabetes. It is intended to provide an indication of when a finger stick may be required, for detecting trends and tracking patterns, and to be used by the Medtronic MiniMed 670G system to

automatically adjust basal insulin levels. The Guardian Sensor (3) is indicated for 7 days of continuous use. The sensor must be calibrated at a minimum of every 12 hours, but it is recommended that the sensor is calibrated 3 or 4 times each day.

Patients must 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 while using the Medtronic MiniMed 670G system. Taking medications with acetaminophen, including, but not limited to Tylenol®, fever reducers, or cold medicine, while wearing the sensor may falsely raise SG readings.

9.1.4.3. Infusion Set Changes

Patients should change their infusion set and reservoir every 3 days.

The patient's study diary will be used to collect unplanned infusion set changes, including date and time of change and the primary reason for unplanned change.

- Pump occlusion alarm,
- Unexplained high BG,
- Infusion site reaction (pain, redness or swelling at infusion site), or
- Infusion set problem (infusion set kinked, pulled out, leaking, reservoir empty, etc.).

Unexplained hyperglycemia is defined as high BG >300 mg/dL that cannot be explained by a missed prior bolus, dietary indiscretion, rebound or treatment of hypoglycemia, a pump failure, an empty pump reservoir, an infusion set complication (for example, kinked, came out, leaking), or an infusion site complication (for example, pain, redness).

Investigators will review pump occlusion alarms, unexplained hyperglycemia, and unplanned 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 change should not be entered as an unplanned infusion set change in the study diary.

9.1.4.4. Diabetes Training

Training will include the following:

- Verify Contour Next LINK meter is paired and communicating with pump
- Frequency of reservoir and infusion set changes
- Frequency of sensor changes
- Infusion site and sensor site rotation
- Responding to pump and sensor alerts and alarms
- Unexplained hyperglycemia management
- Patient's ability to carb count
- Patient's ability use the pump's bolus calculator to determine bolus and correction doses
- Patient's ability to use bolus types appropriately
- Patient's ability to 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 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, the medical device or the study procedures 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 informed consent form (ICF) is signed, study site personnel will record via electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs.

Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, IP, via electronic data entry.

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

A "reasonable possibility" means that there is a cause and effect relationship between the IP, medical 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 department 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 according to SAE-reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

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

Pregnancy (during maternal 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 or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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 guidance.

9.2.2. Complaint Handling

Lilly collects product complaints on IP, materials provided, 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 instructions.

9.3. Treatment of Overdose

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

9.4. Safety

9.4.1. Hypoglycemia

Patients are encouraged to perform SMBG whenever hypoglycemia may be suspected, either by symptoms experienced, CGM reading or perceived increased risk as related to dietary intake, physical activity, inadvertent or atypical insulin dosing or when prompted by pump alerts. All patients will be instructed to consider a BG ≤70 mg/dL to be hypoglycemia and treat appropriately.

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

Hypoglycemia will be described using the following definitions:

- **Documented Glucose Alert (Level 1); BG ≤70 mg/dL:**
  - **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 (Level 2) with similar criterion as above except for threshold BG <54 mg/dL**
  - **Documented symptomatic hypoglycemia**
  - **Documented asymptomatic hypoglycemia**
  - **Documented unspecified hypoglycemia**
- **Severe Hypoglycemia (Level 3):** during these episodes, patients have an altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and the event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose measurements may not be available during such an event, but neurological

recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG ≤70 mg/dL [3.9 mmol/L]).

- **Other Hypoglycemia**
  - **Nocturnal Hypoglycemia:** any documented hypoglycemic event (including severe hypoglycemia) that occurs between bedtime and waking.
  - **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). 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.

Additional analysis of hypoglycemia events will be conducted using CGM data alone for threshold BG <50 mg/dL and <70 mg/dL.

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 on review of the diary and in discussion with the patient, 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).

Electrocardiograms 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.

Electrocardiograms 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. Safety Monitoring

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

9.4.6.1. Pilot Safety Assessment

The pilot safety assessment will take place over 3 days following randomization of the first 10 patients at a single site. During this time, pilot patients must have a designated study companion who is familiar with managing T1D, agree to stay with the patient overnight to assist with checking night-time BG and troubleshooting pump alarms. The designated study companion is not required to accompany the patient during day-time hours.

The investigative site will check in with the patient at Day 1 via a telephone call. During the Visit 5 telephone call, the investigator will review patient data and determine if the patient can continue study treatment.

For 3 nights following the randomization visit (Visit 4), the designated companion must;

- agree to sleep in the same room with the patient,
- sleep within hearing distance of the CGM and pump alarms,
- be willing to awaken at least once between 2:00 AM and 4:00 AM to assist the patient in checking BG ,
- be willing to assist the patient in troubleshooting an alarm if one should occur during the night.

During the Pilot Safety Assessment the Investigative Site will;

- call each pilot patient to check-in within 1 day post randomization visit
- add diary data to eCRF and run a CareLink report for each patient 3 days post randomization visit (Visit 5) enabling the site to;
    - review hypoglycemia, hyperglycemia, occlusion alarm data, and unplanned infusion set changes and reasons
    - discuss other safety issues found in review of SAEs, AEs, Carelink reports, etc.
- decide and document if patient is to continue in the study.

<u>Safety Criteria</u>

The following prespecified criteria will be reviewed by the investigator, along with medical judgment to determine if it is safe to proceed with randomization of additional patients..

- One episode of severe hypoglycemia

- More than 1 case of hyperglycemia (BG >300 mg/dL) sustained for more than 2 hours and unresponsive to treatment measures
- One episode of DKA
- Moderate or large urine ketones and BG >300 mg/dL

Expanding the Pilot Safety Assessment

The pilot safety assessment may be terminated or may be expanded to further understand how LY900014 interacts with the control algorithm in the Medtronic 670G system if any of the above criteria are met or if review of the data collected from SAEs, AEs, Carelink reports, etc. and discussions with patients reveals other safety issues in the judgment of the investigator.

Transition from Pilot Safety Assessment to Rest of the Study

Within 1-week of all 10 pilot patients completing the 3-day pilot safety assessment, the investigators will review the collected data in consultation with the Sponsor and determine if randomization can be opened up for the rest of the study. The 10 pilot patients will continue progressing through the study after completion of the pilot safety assessment so long as they are deemed fit to continue by the site, have had no safety issues that would warrant discontinuation from the study, and no decision has been made to halt the study. No additional patients will be randomized until after a review of pilot safety data occurs and it is decided if continuing the study is warranted. Following the pilot safety assessment, all sites will receive communication from the sponsor to begin randomization of patients not participating in the pilot safety assessment.

9.4.6.2. Hepatic Safety Monitoring

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

Hepatic Safety Data Collection

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

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

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 42 patients will be randomized in order that approximately 36 patients complete the study.

Assuming that a standard deviation (SD) of between-period differences of 10% and a 2-sided alpha level of 0.10, 36 completers will provide approximately 90% power to detect a 5% difference between LY900014 and Humalog, in the percentage of time with SG values from 70 to 180 mg/dL (inclusive), during the last 2 weeks of each 4-week treatment period.

Assuming a 12% dropout rate after randomization, approximately 42 patients (21 patients in each 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 Humalog in the 2-week lead-in period.
Randomized	All patients who are randomly assigned to study treatment at Visit 4 and receive at least 1 dose of the randomly assigned IP. Treatment will be defined on the basis of the treatment the patients are assigned to.

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.

Unless otherwise specified, all efficacy and safety analyses will be conducted on the Randomized Population. Analyses of AEs will include all data collected during the course of the entire 4-week treatment period for each treatment regardless of IP use. Analyses of hypoglycemia will be conducted from first dose to last dose of IP in each 4-week treatment period. Data collected during the safety follow-up period will only be summarized for overall and will not be used for comparisons between treatments.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.10, and confidence intervals (CIs) will be calculated at 90%, 2-sided.

Treatment comparisons will be performed for the primary objective (Section 10.3.3.1) at the full significance level of 0.10. 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 4), unless otherwise specified and described in the SAP.

Unless otherwise specified, a restricted maximum likelihood based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit during the 4-week treatment period for each treatment will be included in the analysis. The model will include the fixed class effects of treatment, period, sequence, strata (HbA1c [≤7.0%, >7.0%] and percentage of time with SG values from 70 to 180 mg/dL over the 2 weeks prior to randomization [≤75%, >75%]), and the continuous, fixed covariate of baseline value. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, a covariance structure of compound symmetry without heterogeneous variances will be used. If the model still does not converge, strata may be deleted from the model. Significance tests will be based on least squares means and Type III tests. SAS PROC MIXED will be used to perform the analysis.

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

10.3.2. Treatment 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 the Randomized Population 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 treatments 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 7.6). No analyses are planned to assess treatment compliance.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to compare LY900014 and Humalog with respect to the percentage of time with SG values within range (70 to 180 mg/dL, both inclusive), during the last 2 weeks of each 4-week treatment period. The analysis model (MMRM) and selection of covariance structure are described in Section 10.3.1.

The primary analyses will be conducted on data collected from the Randomized Population, while patients are on IP and on pump.

10.3.3.2. Secondary Analyses

Additional continuous secondary efficacy variables, as well as the change during each 4-week treatment period for these variables, will be analyzed by the MMRM model described in Section 10.3.1.

10.3.3.3. Exploratory Analyses

Additional continuous exploratory efficacy variables, as well as the change from baseline for these variables, will be analyzed by the MMRM model described in Section 10.3.1, unless otherwise specified.

10.3.4. Safety Analyses

Safety measures will include AEs, hypoglycemia, vital signs, treatment exposure, and laboratory measures.

Events that are newly reported after the first dose of rapid-acting insulin provided as study drug (i.e., open-label Humalog used during the lead-in period or IP used during each of the two 4-week randomized treatment periods) or reported to worsen in severity from baseline (details will be described in SAP) will be considered -TEAEs. Events that continue during more than 1 study period (lead-in, Period I, and Period II) with the same severity will only be counted once for the first study period.

Serious AEs, AEs reported as reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the Medical Dictionary for Regulatory Activities (MedDRA) PT, sorted by decreasing frequency within the LY900014 treated-patients . Treatment-emergent AEs

will also be summarized by PT sorted by decreasing frequency within SOC for all TEAEs and by maximum severity. For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender. The number and proportion of patients with at least 1 event for each type of event will be summarized and compared between treatments using Prescott's exact test.

Hypoglycemia rates will be summarized for periods of 1 year, and 100 years (severe hypoglycemia only) for both treatment periods. Wilcoxon Signed-Rank test and Prescott's exact test will be used instead to analyze the rate and incidence of hypoglycemia events, respectively.

10.3.5. Subgroup Analyses

The following subgroup will be explored to evaluate consistency of treatment effects on the primary endpoint:

- Pump bolus delivery speed at screening (Standard [1.5 U/min], Quick [15 U/min])
- HbA1c stratum (≤7.0%, >7.0%)
- Percentage of time with SG values from 70 to 180 over the 2 weeks prior to randomization (≤75%, >75%)

Additional exploratory subgroup analyses may be performed.

10.3.6. Interim Analyses

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

11. References

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An 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.
AIT	active insulin time
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
blinding	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. 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.
CGM	continuous glucose monitoring
CI	confidence interval
confirmed pump occlusion	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.
CR	carb ratio
CRF	case report form
CRP/CRS	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSII	continuous subcutaneous insulin infusion
CSR	clinical study report
DKA	diabetic ketoacidosis
ECG	electrocardiogram

eCRF	electronic case report form
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IP	investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already 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.
ISF	insulin sensitivity factor
IWRS	interactive web-response system
LS	least squares
MDI	multiple daily injections
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measure
product complaint	Product complaints are a customer's written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution.
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study
SD	standard deviation

SG	sensor glucose
SMBG	self-monitored blood glucose
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which does not necessarily have to have a causal relationship with this treatment
ULN	upper limit of normal
unexplained hyperglycemia	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)

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry (Serum Concentrations of)**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils, segmented	Aspartate aminotransferase (AST)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Uric acid
Basophils	Calcium
Platelets	Chloride
	Magnesium
Urinalysis	Total protein
Specific gravity	Glucose
pH	Albumin
Protein	Creatinine kinase (CK)
Glucose	
Ketones	
Blood	1,5-Anhydroglucitol
Urine leukocyte esterase	Hemoglobin A1c
Bilirubin	
Nitrite	**Serology**
	Pregnancy test (females only)[b]
	Follicle-stimulating hormone[c]

[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.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the 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 informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- 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 must give assurance that the ethical review board (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 Good Clinical Practice (GCP).

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

- the protocol and related amendments and addenda, current IB or Patient Information Leaflet, Package Insert, or Summary of Product Characteristics 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 (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

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

Appendix 3.1.5. Investigator Information

Investigator(s) participating in this study will:

- be a physician with specialty in Endocrinology or Diabetology
- have experience with Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM)
- have clinical trial experience

PPD
Atlanta Diabetes Associates
1800 Howell Mill Rd; Suite #450
Atlanta, GA 30318
PPD

PPD
International Diabetes Center
3800 Park Nicollet Blvd.
Minneapolis, MN 55416
PPD

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 investigator will sign the final clinical study report (CSR) for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

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

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

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

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

Appendix 3.2.1. Data Capture System

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

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

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

Data collected via the sponsor-provided data capture system will be stored with a third party. The investigator will have continuous access to the data during the study and until

decommissioning of the data-capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, 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 or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.4. Publication Policy

The publication policy for Study I8B-MC-ITSM is described in the Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Classification of Contraceptive Methods

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

- Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. 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

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

Appendix 6. Protocol Ammendment I8B-MC-ITSM (b) Evaluation of LY900014 in a Medtronic Pump

Overview

Protocol I8B-MC-ITSM (b) Evaluation of LY900014 in a Medtronic Pump has been amended. The new protocol is indicated by amendment (b) 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-ITSM Amendment (b)

Section # and Name	
Section 6.4 Screen Failures	Section 3.3 Benefit/Risk Assessment Section 5.1 Overall Design Section 9.4.6.1. Pilot Safety Assessment Appendix 3.1.5 Investigator Information
Description of Change	
Added exception for criteria 11b, 11c and 19.	1. changing "single-center" to "multi-center" 2. adding single site to all references to the pilot safety assessment 3. Deleted Investigator address
Brief Rationale	
[11b] and [11c]: Following a 670G system interruption or malfunction, Auto Mode will not activate until the system has completed a warm-up period that lasts between 5 and 48 hours beginning at midnight after the system is restarted. If this occurs during the 4 weeks prior to screening, the percentage of time in Auto Mode and percentage of sensor wear time may be negatively impacted. [19]: The total daily average dose may exceed 100 units/day when carbohydrate consumption is unusually high during the 3 days prior to screening.Allowing for rescreening of patients for whom these criteria apply will potentially increase enrollment of qualified study patients. Lilly believes that allowing these patients to rescreen and subsequently be enrolled will not negatively impact the study because the initial failure was due to a technical or atypical anomaly that has now been corrected.	Due to several factors, including enrollment considerations, the protocol is being amended to change from a single-center to a multi-center study. Several changes in the text capture this transition and also clarify that the pilot safety assessment will be performed at only one site. The implications of the pilot safety assessment apply to all sites. No additional patients will be randomized at any site until the decision of whether to continue the study is made and communicated across sites. Lilly believes that including additional investigative sites in Study ITRO with expertise in the 670G hybrid closed loop system following completion of the pilot safety assessment, will expedite enrollment and as well as leverage the experience and expertise of multiple investigators. Lilly believes adding more sites will not negatively impact the study as the pilot safety assessment will have already been completed at a single site, however, the results will apply to all sites involved in the study.

Revised Protocol Sections

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

Section 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.~~ with the exception of individuals who screen fail due to;

- Inclusion

  [11] Must be using a Medtronic MiniMed 670G insulin pump

  b) In Auto Mode at least an average of 70% of the time per week during the last 4 weeks prior to screening

  c) With a Medtronic Guardian (3) sensor at least an average of 75% of the time per week during the last 4 weeks prior to screening

- Exclusion

  [19] Have a total daily insulin dose >100 units, as determined by the average total daily insulin dose over the 3 days prior to screening.

- Or Combination of any above

If an individual screen fails due to one of the reasons listed, the individual may be rescreened once, no sooner than 2 weeks after the initial screening. Patients who rescreen are not eligible to participate in the pilot safety assessment.

Retests, outside of rescreening, are not allowed, except for cases when results are not available from the original sample. It is expected that any lab or procedure performed in the initial screening be repeated for rescreened patients.

Synopsis Summary of Study Design

This study is a prospective, randomized, double-blind, outpatient, ~~single center,~~ 2-treatment crossover, active-controlled study conducted in patients with type 1 diabetes mellitus (T1D) currently using an external CSII. In the 2 treatment periods, LY900014 and Humalog will be delivered via the Medtronic MiniMed 670G system while in Auto Mode as much as possible.

Synopsis Treatment Arms and Duration

Following the lead-in period, a 3-day pilot safety assessment will be conducted at a single site for the first 10 patients randomized. This pilot safety assessment will determine if the control algorithm in the Medtronic 670G pump can be used safely in patients receiving LY900014.

Section 3.3 Benefit/Risk Assessment

Following the lead-in period, a 3-day pilot safety assessment will be conducted at a single site for the first 10 patients randomized. This pilot safety assessment will determine if the control algorithm in the Medtronic 670G pump can be used safely in patients receiving LY900014.

Section 5.1 Overall Design

This study is a prospective, randomized, double-blind, outpatient, ~~single center,~~ 2-treatment , crossover, active-controlled study conducted in patients with T1D currently using an external CSII pump. In the 2 treatment periods, LY900014 and Humalog will be delivered via the Medtronic MiniMed 670G system with SmartGuard™ technology using AutoMode. In this study, patients will be required to use the Auto Mode insulin delivery function as much as possible.

Following the lead-in period, a 3-day pilot safety assessment will be conducted at a single site in the first 10 patients randomized. This pilot safety assessment will determine if the control algorithm in the Medtronic 670G pump can be used safely in patients receiving LY900014.

Section 9.4.6.1 Pilot Safety Assessment

The pilot safety assessment will take place over 3 days following randomization of the first 10 patients at a single site.

No additional patients will be randomized until after a review of pilot safety data occurs and it is decided if continuing the study is warranted. Following the pilot safety assessment, all sites will receive communication from the sponsor to begin randomization of patients not participating in the pilot safety assessment.

Appendix 3.1.5. Investigator Information

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PPD

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