Protocol I8B-MC-ITSC(a)

A Study to Assess the Pharmacokinetics, Glucodynamics, Safety, and Tolerability of LY900014 in Patients with Type 1 Diabetes Mellitus on Continuous Subcutaneous Insulin Infusion Therapy

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LY900014

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1. Protocol Synopsis

Title of Study: A Study to Assess the Pharmacokinetics, Glucodynamics, Safety, and Tolerability of LY900014 in Patients with Type 1 Diabetes Mellitus on Continuous Subcutaneous Insulin Infusion Therapy

Rationale: This trial is intended to test a new formulation of insulin lispro (LY900014) in patients with type 1 diabetes mellitus (T1DM) using continuous subcutaneous insulin infusion (CSII). The use of LY900014 will be compared to insulin lispro (Humalog® U-100; Reference formulation) when given as a standard dual-wave bolus dose or as a standard (1.5 U/minute) single-wave bolus dose on both Days 1 and 3 and as a rapid (15 U/minute) or standard (1.5 U/minute) single-wave bolus dose on Day 2, with a breakfast meal test using an insulin pump. In addition, rapid versus standard dual-wave bolus doses and rapid versus standard single-wave bolus doses will be compared during the lunch and dinner meals, respectively, using the assigned treatment (LY900014 or Humalog) for that period. Humalog is already marketed and used in diabetes treatment, and its efficacy and safety as a single insulin preparation is well known.

Objectives/Endpoints:

Primary Objectives	**Endpoints**
To evaluate the difference in insulin lispro PK when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	AUC, C_{max}, T_{max}, early 50% T_{max}, and late 50% T_{max}
Secondary Objectives	**Endpoints**
To evaluate the sustainability of any difference in insulin lispro PK of LY900014 and Humalog over 3 days when administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	AUC, C_{max}, T_{max}, early 50% T_{max}, and late 50% T_{max}
To evaluate the difference in GD response when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	ΔAUC
To compare the durability of GD response over 3 days when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	ΔAUC

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum concentration; early 50% T_{max} = time to early half-maximal concentration; GD = glucodynamics; late 50% T_{max} = time to late half-maximal concentration; PK = pharmacokinetics; T1DM = type 1 diabetes mellitus; T_{max} = time to maximum concentration.

Summary of Study Design: This is a single-site, 4-period, patient- and investigator-blind, randomized, crossover study in patients with T1DM to evaluate the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) characteristics of LY900014 (Test) over 3 days with CSII compared with that of Humalog (Reference) using a [redacted].

Each patient will be randomized to 1 of 4 treatment sequences comprising CSII of LY900014 or Humalog, with different combinations of the modes of administration of the bolus doses relative to the breakfast, lunch, and dinner meals using an insulin pump. The modes of administration are as follows:

- Mode 1: bolus dose is administered as a standard dual-wave bolus (50% immediate bolus delivery [speed = 1.5 U/minute] and 50% as a square wave over 3 hours)
- Mode 2: bolus dose is administered as a standard single-wave bolus (speed = 1.5 U/minute)
- Mode 3: bolus dose is administered as a rapid single-wave bolus (speed = 15 U/minute)
- Mode 4: bolus dose is administered as a rapid dual-wave bolus (50% immediate bolus delivery [speed = 15 U/minute] and 50% as a square wave over 3 hours)

A mixed-meal tolerance test (MMTT) will be administered at breakfast as an individually standardized solid test meal on Day 1 and Day 3 and as a high-glycemic index test meal on Day 2. The assigned treatment will be administered as a bolus dose at time 0 relative to the start of each breakfast test meal via 3 different modes: Modes 1, 2, and 3.

An individually standardized solid lunch will be administered on Days 1, 2, and 3. The assigned treatment will be administered as standard (Mode 1) or rapid (Mode 4) dual-wave bolus doses at time 0 relative to the start of each lunch meal.

An individually standardized dinner will be administered on Days 1 and 2. The assigned treatment will be administered as standard (Mode 2) or rapid (Mode 3) single-wave bolus doses at time 0 relative to the start of each dinner meal.

Treatment Arms and Duration: Patients will be randomly assigned to 1 of 4 dosing sequences; each sequence will have 4 periods. Patients will be administered bolus doses of LY900014 or Humalog during the 3-day inpatient stay for each study period and bolus doses of Humalog for the lead-in and outpatient time periods.

Number of Patients: Initially, 24 patients will be enrolled to target approximately 20 patients to complete all 4 periods of the study. Patients who drop out may be replaced, up to a maximum of 30 total patients enrolled, to ensure 20 completers; the replacement patient will adopt all assigned treatments of the original patient's randomization schedule and complete all 4 study periods.

Statistical Analysis:

Primary statistical analyses will be conducted on the set of patients receiving at least 1 dose of the study drug to which they are randomized. Patients who complete at least 1 MMTT and have measurable insulin lispro concentrations will be included in the analysis dataset for the PK analyses. Patients who receive at least 1 dose of study drug and have evaluable GD data will be included in the analysis set for the GD analyses.

Sample Size: Twenty completing patients will provide approximately 80% power to demonstrate a 25% decrease in the time to early half-maximal concentration (early 50% T_{max}) between LY900014 and Humalog. Testing will be done at an α-level of 0.1 with a 2-sided confidence interval (CI). The variability was estimated as approximately 35.9% coefficient of variation of within-subject variability for early 50% T_{max}.

Safety: All treatment- (investigational product and Humalog noninvestigational product) and procedure-related adverse events (AEs) will be listed, and if the frequency of events allows, safety data will be summarized using

descriptive methodology. The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. The number of investigational product-related serious AEs (SAEs) will be reported. Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics.

Pharmacokinetics: PK analyses will be conducted using standard noncompartmental methods of analysis. Serum insulin lispro concentrations will be used to calculate several PK parameters, including time to maximum concentration (T_{max}), early 50% T_{max}, time to late half-maximal concentration (late 50% T_{max}), maximum concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from time 0 to 15 minutes postdose (AUC[0-15min]), AUC from time 0 to 30 minutes postdose (AUC[0-30min]), AUC from time 0 to 1 hour postdose (AUC[0-1h]), AUC from time 0 to the last recorded time (AUC[0-t_{last}]), and AUC from time 0 to 5 hours postdose (AUC[0-5h]).

Log-transformed insulin lispro T_{max}, early 50% T_{max}, late 50% T_{max}, C_{max}, and AUC estimates will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog, and the corresponding 90% CIs of the ratios.

The statistical model for Days 1 and 3 breakfast meal tests will include treatment (4 combinations of treatment and bolus administration mode), period, day-within-period, and treatment-by-day-within-period interaction as fixed effects and patient as a random effect. A separate analysis model will be used for the Day 2 breakfast meal test, including treatment (4 combinations of treatment and bolus administration mode) and period as fixed effects and patient as a random effect. For the primary inference, insulin lispro administered from LY900014 will be concluded to have a significantly decreased early 50% T_{max} relative to Humalog if the upper confidence bound of the 2-sided 90% CI of the ratio of geometric means of the early 50% T_{max} is <1. As a sensitivity analysis, early 50% T_{max} will be analyzed using the Wilcoxon signed-rank test.

Glucodynamics: Data will be analyzed for the patients during each MMTT. The change from baseline values for each patient will be calculated. Incremental change from baseline glucose AUC values will be calculated during a 5-hour meal test.

Summary statistics will be presented by treatment and by bolus dose administration mode (all 4 combinations of treatment) for Days 1 and 3 and Day 2, separately. The same statistical model and comparisons used to analyze the PK parameters will be used to analyze the GD parameters on the original scale (not log-transformed) using Fieller's theorem.

Exploratory Continuous Glucose Monitoring: The continuous glucose monitoring (CGM) outcome variables (for example, incremental change from baseline AUC[0-5h], the change from baseline 1- and 2-hour excursions) will be derived based on the raw data collected from the individualized standardized lunch meals on Days 1, 2, and 3 and from the individualized standardized dinner meals on Days 1 and 2.

Immunogenicity: The relationship between the status (positive or negative) of treatment-emergent anti-insulin lispro antibodies and treatment-emergent AEs (TEAEs) will be assessed. Likewise, the relationship between the status of treatment-emergent antibodies and the PK parameters and GD response to insulin lispro may also be assessed.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITSC

Procedure	Screen[a] Days -28 to -8	Lead-In Days -7 to -1	Periods 1 to 4				ED/ FU[a,b]	Comments
			Day -1	Day 1	Day 2	Day 3		
Informed consent	X							At least 1 day before screening procedures. Screening procedures should take place no later than 28 days after signing the informed consent.
Physical examination/medical assessment	X		X			Before discharge from CRU	X	Physical examination and medical history at screening. Thereafter, medical review and targeted examination, as appropriate, including review of patient diary.
AE and concomitant medication	X		X	X	X	X	X	
Height and weight	X						X	Height will be measured at screening only.
Eligibility assessment	X		X					Meal test exclusion criteria (Section 6.3.1) will be reviewed on Day −1 at admittance to the CRU.
Lead-in activities		X						Patients will switch from their short-acting insulin used before the start of the study to Humalog; patients will continue to use their own pump to administer Humalog. A patient diary will be provided for recording dosing and any information as required by the investigator (refer to Section 5.1 for a detailed description).
Training		X				X		Diabetes training will include dose calculation for short-acting insulins; correct self-monitoring of plasma glucose; and interpretation of results, symptoms, and treatment of hypoglycemia.
Admission to CRU			X					Will be admitted to CRU in the early evening (approximately 5:00 PM).
Discharge from CRU						X		Patients will be discharged from the CRU at least 5 hours after the start of the lunch meal.

Procedure	Screen[a] Days -28 to -8	Lead-In Days -7 to -1	Periods 1 to 4				ED/ FU[a,b]	Comments
			Day -1	Day 1	Day 2	Day 3		
Insert CGM			X					The CGM system will be inserted before the start of the Day –1 standardized dinner.
Standardized dinner			X					Approximately 7:00 PM and should be consumed within 20 minutes. Identical to the standardized test dinner served on Days 1 and 2.
Catheter insertion/change			X			X		Day –1: after the standardized dinner. Day 3: after the lunch meal procedures (blood draws and medical assessments) are completed (approximately 5 hours after the start of the lunch meal), unless the patient stays at the clinic until that evening (approximately 5:00 PM) for Day –1 procedures for next period; then the new catheter will be inserted after the standardized dinner (Day –1 for the following period).
Run-in/stabilization of glucose				X (approximately 1:00 AM)		X (approximately 1:00 AM)		From 7 hours to 30 minutes before dosing: infusion of glucose (dextrose solution) or insulin [redacted] to target a plasma glucose concentration of 126 mg/dL (7.0 mM). Run-in/stabilization of glucose will begin at approximately 1:00 AM. Plasma glucose concentrations will be monitored approximately every 30 minutes.
Glucose monitoring before Day 2 meal test					X			After completion of the standardized dinner to 30 minutes before dosing: plasma glucose concentrations will be monitored approximately every hour.

Procedure	Screen[a] Days -28 to -8	Lead-In Days -7 to -1	Periods 1 to 4				ED/ FU[a,b]	Comments
			Day -1	Day 1	Day 2	Day 3		
Glucose monitoring throughout inpatient period			X	X	X	X		Regular monitoring of blood glucose using the CCI [redacted] (approximately every 2 hours) will also be performed during the complete inpatient period outside of the breakfast meal test procedures and includes predose before the standardized lunch and dinner.
Treatment administration (LY900014 or Humalog)			X	X	X	X		Day –1 prandial Humalog shall be administered using the patient's own personal pump. After the standardized dinner the patient will switch to the CCI [redacted]; the reservoir will be filled with the assigned study treatment (LY900014 or Humalog) by qualified staff. Study treatment will be administered continuously via a basal infusion and via a bolus dose immediately before each breakfast test meal and standardized lunch meal (Days 1, 2, and 3) and before each standardized dinner meal (Days 1 and 2 only), which should follow within 1 minute of dosing.
Breakfast test meals (refer to Sections 6.3.1.1 and 6.3.1.2)				X (MMTT)	X (high-glycemic index meal test)	X (MMTT)		Breakfast (Days 1, 2, and 3) will be given immediately after dosing (approximately 8:00 AM) and should be consumed within 20 minutes on Days 1 and 3 and within 15 minutes on Day 2.
Standardized test lunch (refer to Section 6.3.1.3)				X	X	X		Approximately 1:00 PM and at least 5 hours after the start of the breakfast meal; the meal should be consumed within 20 minutes.
Standardized test dinner (refer to Section 6.3.1.3)				X	X			Approximately 7:00 PM and at least 5 hours after the start of the lunch meal; the meal should be consumed within 20 minutes.

Procedure	Screen[a] Days -28 to -8	Lead-In Days -7 to -1	Periods 1 to 4				ED/ FU[a,b]	Comments
			Day -1	Day 1	Day 2	Day 3		
Remove CGM						X		After the Day 3 lunch meal procedures are completed (approximately 5 hours after the start of the lunch meal), the CGM system will be removed.
Vital signs[c] (minutes)	X		X	X (predose, 30, 120)	X (predose, 30, 120)	X (predose, 30, 120, and before discharge from CRU)	X	Blood pressure and pulse rate should be measured after at least 5 minutes supine; body temperature at screening only. Time is referenced to bolus dose of insulin lispro (LY900014 or Humalog) for the breakfast meal tests, that is, time 0.
12-lead ECG[c]	X			X (predose, Period 1 only)		X (predose, Period 1 only)	X	Single ECGs only. ECGs should be recorded before collecting any blood for safety or PK tests.
Clinical laboratory tests[c]	X			Period 1 only (predose)			X	Details in Appendix 2 (Clinical Laboratory Tests).
Alcohol breath test			X					May be repeated before every CRU admission. The alcohol breath test is included in the Day –1 eligibility assessment.
Pregnancy test/urine drug screen	X		X				X	Pregnancy test will be taken for female patients only. Serum pregnancy test at screening. Urine pregnancy test for all other visits.
Insulin lispro PK sampling (minutes)				-15, 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300	-15, 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300	-15, 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300		Time is referenced to the start of the administration of the bolus dose of insulin lispro (LY900014 or Humalog) for the breakfast meal tests, that is, time 0.

Procedure	Screen[a] Days -28 to -8	Lead-In Days -7 to -1	Periods 1 to 4				ED/ FU[a,b]	Comments
			Day -1	Day 1	Day 2	Day 3		
Plasma glucose monitoring with ~~Super GL glucose analyzer~~ (minutes)				-30, -15, 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300	-30, -15, 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300	-30, -15, 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300		Time is referenced to the start of the administration of the bolus dose of insulin lispro (LY900014 or Humalog) for the breakfast meal tests, that is, time 0.
VAS and insertion-site assessments (minute)				0[d], 20, 40, 60, 120, 180, 240, 300	0[d], 20, 40, 60, 120, 180, 240, 300	0[d], 20, 40, 60, 120, 180, 240, 300		Time is referenced to dose of insulin lispro (LY900014 or Humalog) for the breakfast test meals.
Assessment of insulin delivery experience						X		Subjects will be asked to provide the overall acceptability of their insulin delivery experience, either prior to CRU discharge or after completing Day 3 lunch procedures for each period.
Biomarker sample[c] (PGx)				Period 1 only (predose)				
Sample for immunogenicity[c]				Period 1 only (predose)			X	Additional samples may be collected if there is a possibility that an AE is immunologically mediated.

Abbreviations: AE = adverse event; CGM = continuous glucose monitoring; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; MMTT = mixed-meal tolerance test; PK = pharmacokinetics; VAS = visual analog scale.

Note: Interim telephone visits may occur at any time during the outpatient periods, as determined by the investigator, to review the safety and well-being of the patient.

a Patients should be fasted for at least 8 hours before the start of screening and follow-up (or early discontinuation) activities. Patients may consume up to 20 g of carbohydrates to treat or prevent hypoglycemia during the fasting periods.

b Within 7 to 14 days after last dose or early discontinuation.

c Predose is defined as the predose for the breakfast test meal only. Predose measurements should be performed within approximately 2 hours before the planned dosing time.

d The VAS at the 0-minute time point is to be performed as soon as practicably possible after the start of the dosing for the breakfast meal tests.

3. Introduction

3.1. Study Rationale

There is an unmet medical need for fast prandial insulin analogs with improved pharmacokinetic (PK) and glucodynamic (GD) characteristics.

A new formulation of insulin lispro will be used in this study and was developed as an ultra-rapid–acting insulin formulation with an even faster onset of action than currently available rapid-acting insulin analogs. The changes in PK and GD characteristics are achieved by coformulating insulin lispro with a microdose of treprostinil (the active ingredient in CCI [redacted]) and Generally Recognized as Safe (GRAS) excipients.

This trial is intended to test this new formulation of insulin lispro (LY900014) in patients with type 1 diabetes mellitus (T1DM) using continuous subcutaneous insulin infusion (CSII). Different insulin pump–delivered bolus options are assessed in this study: a single-wave bolus provides a single immediate dose of insulin in 2 speed options (rapid [15 U/minute] or standard [1.5 U/minute]), and a dual-wave bolus delivers a combination of an immediate single-wave bolus (either standard or rapid) followed by a square-wave bolus (a single bolus administered evenly over an extended period of time). The use of LY900014 will be compared to insulin lispro (Humalog® U-100; Reference formulation) when given as a standard dual-wave bolus dose or as a standard (1.5 U/minute) single-wave bolus dose on both Days 1 and 3, and as a rapid (15 U/minute) or standard (1.5 U/minute) single-wave bolus dose on Day 2, with a breakfast meal test using an insulin pump. In addition, rapid versus standard dual-wave bolus doses and rapid versus standard single-wave bolus doses will be compared during the lunch and dinner meals, respectively, using the assigned treatment (LY900014 or Humalog) for that period. Humalog is already marketed and used in diabetes treatment, and its efficacy and safety as a single insulin preparation is well known.

This clinical trial will be conducted to gather PK/GD, safety, and compatibility (that is, catheter occlusions) data on LY900014 when used in CSII therapy with a pump and administered as either standard or rapid dual-wave or single-wave bolus doses on Days 1, 2, and 3.

A study using model-predicted optimized bolus delivery has shown that a bolus for a mixed meal containing a substantial amount of fat (approximately 40% of total calories), compared to a meal with the same carbohydrate content but only a minimal amount of fat, needs a larger bolus dose and a dual-wave delivery method to achieve optimal postprandial glucose control (Bell et al. 2016). Therefore, testing a dual-wave bolus dose and different bolus speed options to support a safe and efficient use of LY900014 in T1DM patients using an insulin pump is of great clinical interest.

3.2. Background

A prandial insulin with faster-on and/or faster-off characteristics might reduce glycemic excursions and the incidence of late postprandial hypoglycemia compared to currently available fast-acting insulin analogs. The insulin analog, insulin lispro (Humalog), has been shown to be absorbed more quickly than regular human insulin (Humalog package insert 2015). In healthy

subjects given subcutaneous (SC) doses of insulin lispro ranging from 0.1 to 0.4 U/kg, peak serum levels were seen 30 to 90 minutes after dosing. Insulin analogs are absorbed faster than human insulin; however, the general consensus is that rapid-acting insulin, administered either by pumps or syringes/pen injectors, is still not rapid enough to match carbohydrate absorption profiles, limiting efficacy and dosing flexibility. It is anticipated that an ultra-rapid–acting prandial insulin would shift the PK/GD of insulin analogs so that they have an even faster onset to match carbohydrate absorption and also allow greater flexibility and postmeal dosing. This ultra-rapid insulin (URI) could be for use in T1DM and type 2 diabetes mellitus (T2DM) in adults and children when given by multiple daily injections (MDI) or by CSII. A URI could be created by using additives that increase local capillary blood flow and/or alter vascular permeability.

This study aims to characterize the PK of insulin lispro after administration of LY900014, which is a formulation of insulin lispro, treprostinil, and other excipients using an insulin pump. This formulation involves the novel use of a microdose of treprostinil (CCI as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than an active pharmaceutical ingredient to elicit a systemic effect. LY900014 (Test formulation) is considered the investigational medicinal product (IMP) for this study.

Treprostinil is a prostacyclin analog, administered either by inhalation (CCI), as an intravenous (IV) infusion, or as a continuous SC infusion for the treatment of symptomatic pulmonary arterial hypertension (PAH), and has been approved in the United States since 2002 (CCI) and in Germany since 2006 (CCI . Sodium citrate and each of the other excipients (zinc chloride, magnesium chloride, glycerin, and m-cresol) in the LY900014 formulation are listed in the Food and Drug Administration (FDA) GRAS food additives database (FDA SCOGS [WWW]) and in the FDA Inactive Ingredients in Approved Drugs database (FDA [WWW]). Furthermore, the excipient concentration in LY900014 is within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

3.2.1. Clinical Studies

Five clinical studies were conducted that evaluated the effects of administration of treprostinil alone, insulin lispro formulated with treprostinil, and LY900014: CCI All 5 studies are complete (refer to the LY900014 Investigator's Brochure [IB] for detailed information).

The PK of treprostinil following SC bolus injection has been assessed across the 5 Phase 1a clinical studies listed above. The treprostinil concentration versus time profile and PK parameters were consistent across studies, and treprostinil was rapidly absorbed and eliminated following SC bolus administration (refer to the IB). If treprostinil levels were detectable at doses of CCI , these observations were approximately the maximum concentration (C_{max}) and were slightly above the detection limit of the assay (CCI); no changes in blood pressure or pulse rate that might suggest systemic effects of treprostinil were observed.

Treprostinil exposure following LY900014 administration was monitored in the 3 ongoing Phase 1b studies (Studies [CCI redacted], and I8B-[CCI redacted]) which evaluated the PK, GD, safety, and tolerability of MDIs of LY900014 in patients with T1DM and T2DM and when used in patients with T1DM using CSII. Treprostinil exposure was assessed at 15 minutes and 30 minutes postdose (approximately C_{max}) in the Phase 1b MDI studies and throughout the duration of the CSII for each period in all patients who were administered LY900014. Preliminary data analysis showed that only 1 sample had detectable treprostinil drug concentration levels in plasma from the approximately 967 samples taken from a total of 75 T1DM and T2DM patients following MDI administration of LY900014 using doses up to 40 U per SC bolus injection containing approximately [CCI redacted] of treprostinil. Importantly, no detectable drug levels were observed with CSII therapy in 30 patients.

The estimated total daily treprostinil (basal and bolus) doses in LY900014 for patients with T1DM in this study are expected to be within the clinical dose range previously explored with SC bolus administration of treprostinil. The highest daily insulin lispro/treprostinil doses are expected to be administered to patients with T2DM with MDI therapy. Based on the estimated amount of treprostinil delivered from relatively large preprandial bolus doses of LY900014 in patients with T2DM ([CCI redacted] [with 50 U insulin lispro]) and the lack of treprostinil exposures observed in the 3 Phase 1b studies, treprostinil concentrations during use of LY900014 in CSII therapy are expected to be minimal or undetectable.

All tested doses of treprostinil and insulin lispro were well tolerated in both healthy subjects ([CCI redacted]) and patients with T2DM ([CCI redacted]). There were no serious adverse events (SAEs) related to study treatment in any of the 5 completed studies. No subject discontinued from the studies because of a drug-related adverse event (AE).

In a preliminary review of data from 3 ongoing Phase 1b PK and GD studies ([CCI redacted]), LY900014 was well tolerated in patients with T1DM using MDI or insulin pump treatment and T2DM using MDI. There were no SAEs related to study treatment or discontinuations from the studies because of a drug-related AE. Small numbers of treatment-emergent AEs (TEAEs) were reported, and there were no notable increases in these events in relation to any of the LY900014 formulations compared to those in relation to Humalog. No significant differences were observed for injection-site tolerability and hypoglycemic events when LY900014 was compared to Humalog.

More information about the LY900014 clinical studies are to be found in the IB.

3.3. Benefit/Risk Assessment

The data from previous studies ([CCI redacted]) and preliminary data from ongoing studies ([CCI redacted] [MDI] and Study [CCI redacted] [CSII]) have shown that LY900014 was well tolerated and the adverse drug reactions are in keeping with those reported for Humalog.

Potential risks associated with LY900014, derived from the known risks of insulin lispro (Humalog) which is the active pharmaceutical ingredient in LY900014, are hypoglycemia, hypersensitivity reactions (localized allergy and/or systemic allergy), undesirable effects at the

injection site (injection-site reactions and lipodystrophy), and peripheral edema (Humalog package insert 2015).

Notably, across all doses in the Lilly clinical studies that have evaluated treprostinil as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those AEs associated with systemic absorption of treprostinil, as described in the CCI [redacted]) (that is, headache, diarrhea, nausea, jaw pain, vasodilatation, rash, edema, anorexia, vomiting, asthenia, abdominal pain, and hypotension). The exposures of treprostinil in LY900014 for participants in this study are expected to be undetectable based on preliminary data from CCI [redacted]. The dose ranges previously explored with SC bolus administration of treprostinil resulted in treprostinil exposures that were undetectable or substantially lower than those observed for the treatment of PAH.

No additional potential risks of LY900014 or treprostinil alone were identified in preclinical safety pharmacology and toxicity studies or clinical pharmacology studies. No known potential risks are associated with the use of small amounts of treprostinil (CCI [redacted]) in the LY900014 formulation.

Additionally, local and systemic toxicity profiles of Humalog and CCI [redacted] do not suggest the potential for additive or synergistic toxicity.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY900014 may be found in the IB.

More detailed information about the known and expected benefits and risks of Humalog may be found in the Summary of Product Characteristics (Humalog: EPAR [WWW]); known and expected benefits and risks of treprostinil may be found in the package insert for treprostinil (CCI [redacted]).

4. Objectives and Endpoints

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

Table ITSC.4.1. Objectives and Endpoints

Primary Objective	**Endpoints**
To evaluate the difference in insulin lispro PK when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	AUC, C_{max}, T_{max}, early 50% T_{max}, and late 50% T_{max}
Secondary Objectives	**Endpoints**
To evaluate the sustainability of any difference in insulin lispro PK of LY900014 and Humalog over 3 days when administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	AUC, C_{max}, T_{max}, early 50% T_{max}, and late 50% T_{max}
To evaluate the difference in GD response when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	ΔAUC
To compare the durability of GD response over 3 days when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test	ΔAUC
Exploratory Objectives	**Endpoints**
To evaluate the safety and tolerability of LY900014 administered with an insulin pump	Adverse events, anti–insulin lispro antibodies, infusion-site reactions/pain, and frequency and/or severity of hypoglycemia
To compare the GD response using CGM when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a standardized lunch meal	ΔAUC
To compare the GD response using CGM when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a standardized dinner meal	ΔAUC
To evaluate the intrasubject and intersubject insulin lispro PK variability of LY900014 compared with Humalog after 3 days of CSII	CV of AUC
To determine catheter occlusion rates with LY900014 and Humalog after 3 days of CSII	Microscopic assessment of infusion tubing after 3 days of use or in case of suspected catheter occlusion
To perform an exploratory comparison of glucose fluctuations with time in patients with euglycemia, hypoglycemia, and hyperglycemia receiving LY900014 and Humalog	CGM profiles during inpatient periods: time in euglycemia, hypoglycemia, and hyperglycemia

Abbreviations: AUC = area under the concentration versus time curve; CGM = continuous glucose monitoring; C_{max} = maximum concentration; CSII = continuous subcutaneous insulin infusion; CV = coefficient of variation; early 50% T_{max} = time to early half-maximal concentration; GD = glucodynamics; late 50% T_{max} = time to late half-maximal concentration; PK = pharmacokinetics; T1DM = type 1 diabetes mellitus; T_{max} = time to maximum concentration.

5. Study Design

5.1. Overall Design

This is a single-site, 4-period, patient- and investigator-blind, randomized, crossover study in patients with T1DM to evaluate the insulin lispro PK and GD characteristics of LY900014 (Test) over 3 days with CSII compared with that of Humalog (Reference) using a CCI [redacted].

Each patient will be randomized to 1 of 4 treatment sequences comprising CSII of LY900014 or Humalog, with different combinations of the modes of administration of the bolus doses relative to the breakfast, lunch, and dinner meals using an insulin pump (refer to Figure ITSC.5.1 and Table ITSC.5.1). The modes of administration are as follows:

- Mode 1: bolus dose is administered as a standard dual-wave bolus (50% immediate bolus delivery [speed = 1.5 U/minute] and 50% as a square-wave over 3 hours)
- Mode 2: bolus dose is administered as a standard single-wave bolus (speed = 1.5 U/minute)
- Mode 3: bolus dose is administered as a rapid single-wave bolus (speed = 15 U/minute)
- Mode 4: bolus dose is administered as a rapid dual-wave bolus (50% immediate bolus delivery [speed = 15 U/minute] and 50% as a square wave over 3 hours)

The compositions of the meals are described in Section 6.3.1.

A mixed-meal tolerance test (MMTT) will be administered at breakfast as an individually standardized solid test meal on Day 1 and Day 3 and as a high-glycemic index test meal on Day 2. The assigned treatment will be administered as a bolus dose at time 0 relative to the start of each breakfast test meal via 3 different modes: Modes 1, 2, and 3.

An individually standardized solid lunch will be administered on Days 1, 2, and 3. The assigned treatment will be administered as standard (Mode 1) or rapid (Mode 4) dual-wave bolus doses at time 0 relative to the start of each lunch meal.

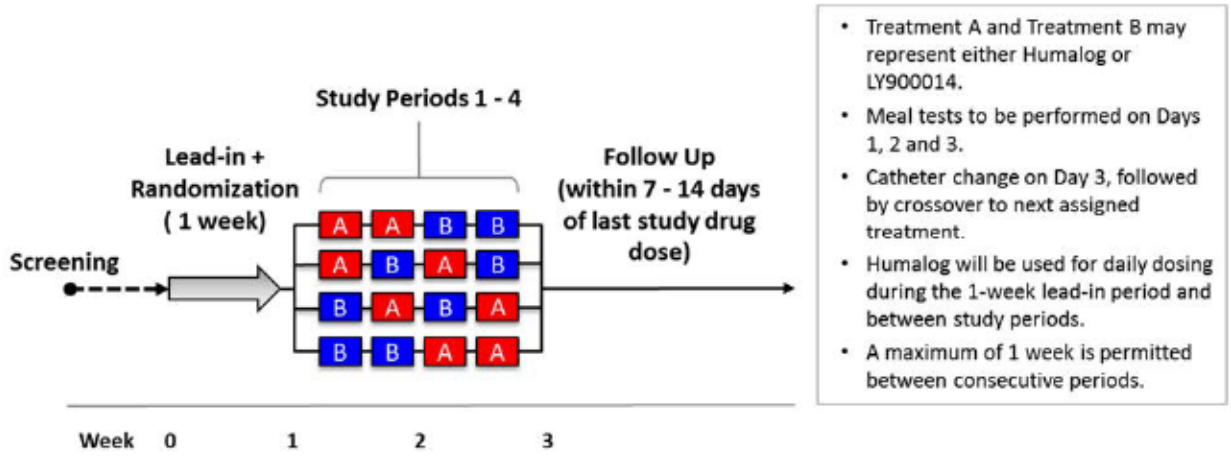
An individually standardized dinner will be administered on Days 1 and 2. The assigned treatment will be administered as standard (Mode 2) or rapid (Mode 3) single-wave bolus doses at time 0 relative to the start of each dinner meal.

The study design is shown in Figure ITSC.5.1 and planned treatment sequences are shown in Table ITSC.5.1. Details of the inpatient and outpatient procedures are described in Section 5.1.1 and Section 5.1.2, respectively.

Patients who are eligible to participate in the study based on the results of the screening procedures will proceed to a 1-week lead-in period. During the lead-in period, patients will (if not receiving Humalog) switch from their short-acting insulin used before the start of the study

to Humalog, which will be administered using their own personal pump. Patients will also be provided with a general diabetes training including, but not limited to, dose calculation for short-acting insulins; correct self-monitoring of plasma glucose; and interpretation of results, symptoms, and treatment of hypoglycemia. A patient diary will also be provided for documentation of dosing, meals, and glucose monitoring outcomes.

Patients will be randomly assigned to a treatment sequence according to the actual randomization schedule provided to the site at the beginning of or during the lead-in period. The CCI [redacted] pump will be used for all study treatment administrations, while maintaining the catheter needle at the same catheter insertion-site location for the 3-day duration of each study period. Before each MMTT on Day 1 and Day 3, a run-in period to stabilize plasma glucose levels will occur. Details of run-in activities are described in Section 5.1.1.2 and Section 2. Before the breakfast meal test on Day 2, the patients will have their plasma glucose monitored approximately every hour during the night to ensure that the targeted plasma glucose range is met before the start of the Day 2 meal test.



Note: Patients will be randomized to 1 of 4 treatment sequences; each sequence has 4 periods. Each period comprises dosing with assigned treatment (Humalog or LY900014) over Days 1 to 3.

Figure ITSC.5.1. Study design.

Patients will be required to attend the clinical research unit (CRU) on at least 8 occasions:

- a visit for informed consent
- a screening visit (may occur up to 21 days before the lead-in period)
- an initial CRU visit at the start of the 1-week lead-in period in which all patients will receive Humalog as their CSII
- 4 inpatient stays from Day –1 to Day 3 (one in each study period)
- a follow-up visit (within 7 to 14 days after the last dose or early discontinuation)

Table ITSC.5.1. Planned Treatment Sequences by Period

Treatment Sequence	Meal	Period 1			Period 2			Period 3			Period 4		
		Days			Days			Days			Days		
		1	2	3	1	2	3	1	2	3	1	2	3
1		Treatment A			Treatment A			Treatment B			Treatment B		
	Breakfast	SD	RS	SD	SS	SS	SS	SD	RS	SD	SS	SS	SS
	Lunch	RD	RD	RD	SD	SD	SD	RD	RD	RD	SD	SD	SD
	Dinner	SS	SS		RS	RS		SS	SS		RS	RS	
2		Treatment A			Treatment B			Treatment A			Treatment B		
	Breakfast	SS	SS	SS	SS	SS	SS	SD	RS	SD	SD	RS	SD
	Lunch	SD	SD	SD	SD	SD	SD	RD	RD	RD	RD	RD	RD
	Dinner	RS	RS		RS	RS		SS	SS		SS	SS	
3		Treatment B			Treatment A			Treatment B			Treatment A		
	Breakfast	SD	RS	SD	SD	RS	SD	SS	SS	SS	SS	SS	SS
	Lunch	RD	RD	RD	RD	RD	RD	SD	SD	SD	SD	SD	SD
	Dinner	SS	SS		SS	SS		RS	RS		RS	RS	
4		Treatment B			Treatment B			Treatment A			Treatment A		
	Breakfast	SS	SS	SS	SD	RS	SD	SS	SS	SS	SD	RS	SD
	Lunch	SD	SD	SD	RD	RD	RD	SD	SD	SD	RD	RD	RD
	Dinner	RS	RS		SS	SS		RS	RS		SS	SS	

Note: Patients will be randomized to 1 of 4 treatment sequences, each comprising different administration modes for the prandial bolus dose for the breakfast, lunch, and dinner meals on Days 1 through 3 in each of the 4 periods.

"Treatment A" and "Treatment B" may represent either Humalog or LY900014. Patients will be assigned a treatment sequence according to the actual randomization schedule provided to the site.

Bolus dose administration modes: RD = rapid dual-wave; RS = rapid single-wave; SD = standard dual-wave; SS = standard single-wave.

Patients will be discharged from the CRU on Day 3 (at least 5 hours after the start of the lunch meal) or later, if deemed necessary for safety monitoring as determined by the investigator. Study treatments may be administered on consecutive days from one period to the next, and a maximum time of 1 week is permitted between consecutive periods.

Patients will continue their individual CSII basal rate using the insulin pump during the entire study including the meal test days unless safety issues arise; in this case, the investigator will discuss a change of the basal rate with the sponsor clinical research physician (CRP) and implement this change, if necessary, to prevent any medical problems. However, during the MMTT (approximately 6:00 AM to 2:00 PM on Days 1 and 3) and the high-glycemic index breakfast meal test (approximately 6:00 AM to 2:00 PM on Day 2), the basal rate will be changed to a single hourly rate based on the patient's mean basal needs during the meal test period. For all lunch and dinner meals during the inpatient periods, the patients' individual CSII basal rate will be continued unchanged.

Assessment of local tolerability at all catheter insertion sites will be performed as specified in the Study Schedule (Section 2), including visual analog scale (VAS) scores for pain and inspection of the catheter insertion site for signs such as edema, erythema, and rash.

For each meal test day (Days 1, 2, and 3), serial blood samples will be collected over approximately 300 minutes to assess the PK and GD responses following start of the breakfast

meal test, as specified in the Study Schedule (Section 2). For each standardized lunch and dinner meal on Days 1 through 3, the GD response will be assessed using continuous glucose monitoring (CGM) following start of the meals.

5.1.1. Inpatient Procedures

Patients will arrive at the CRU in the early evening of Day –1 (approximately 5:00 PM), and a CGM system will be inserted before the start of a standardized dinner (at approximately 7:00 PM). A standard system will be used for CGM (for example, CCI [redacted]). The patients will wear this device during all inpatient days. The CGM device will be calibrated using the plasma glucose values obtained with the CCI [redacted] by site personnel. Regular monitoring of blood glucose using the CCI [redacted] (approximately every 2 hours) will be performed during the complete inpatient period outside of the breakfast meal test procedures.

The catheter needle will be inserted during the evening of Day –1 and should stay at the same catheter insertion-site location for the duration of each period (3 days). If the patient needs to change the catheter during the study period (between Day 1 to Day 3), the patient may repeat that study period once only if the maximum blood loss over the entire study (that is, the blood loss during the past periods and the expected blood loss of upcoming periods) will not exceed approximately 550 mL. The patient will not be withdrawn from the study even if the period cannot be repeated.

A breakfast MMTT of fixed nutrient composition will be administered on Day 1 and Day 3, and a high-glycemic index breakfast test meal will be administered on Day 2 for each of the 4 treatment periods. Additionally, a standardized lunch will be administered on Days 1, 2, and 3, and a standardized dinner will be administered on Days 1 and 2. A detailed description of the test meals is presented in Section 6.3.1. Patients will be without further oral food intake from the start of each meal to completion of blood collection for the breakfast meals and to 5 hours after the start of the meal for the lunch and dinner meals (approximately 300 minutes) unless required to treat hypoglycemia, as defined by a plasma glucose level <56 mg/dL (3.1 mM) or symptoms that require treatment as assessed by the investigator during the inpatient period that is reversed with either rapidly absorbable oral carbohydrates or IV glucose. If a patient's plasma glucose concentration rises above 306 mg/dL (17 mM) for more than 1 hour, insulin glulisine (CCI [redacted]) will be administered IV. In both cases, blood samples for plasma glucose (for safety) will be taken, and PK samples will be collected as planned.

All LY900014 and Humalog doses for standardized meals as well as for snacks outside of the defined postmeal assessment periods will be administered by qualified site staff using a CCI [redacted] pump during the inpatient period (Day –1, starting after the administration of the standardized dinner, and continuing to Day 3). Patients will use their own personal pump to administer Humalog during the lead-in and outpatient periods, including the Day –1 prandial Humalog dose taken before the start of the standardized dinner.

5.1.1.1. Day –1 Study Activities

On Day –1 in each of the 4 periods, patients will arrive at the CRU in the early evening (at approximately 5:00 PM), and a CGM system will be inserted. The patient's short-acting insulin (Humalog) may be administered with their own pump before the start of a standardized dinner (at approximately 7:00 PM). After the standardized dinner, the CCI pump reservoir will be filled by a qualified site staff member with either LY900014 or Humalog, and a standard infusion set and catheter will be inserted after a priming dose has been given to test the catheter. The catheter should remain unchanged from approximately 8 hours before the start of the breakfast meal on Day 1 to approximately 5 hours after the start of the lunch meal on Day 3. In case of immediate infusion set intolerance, a new needle can be inserted up until 7 hours before bolus dosing. Up to 6 U of LY900014 or Humalog may be administered as a bolus with the pump between 7 and 12 hours before the scheduled meal test. Before the start of a run-in period, the cannulation of 2 veins will be performed.

5.1.1.2. Day 1 Study Activities

On Day 1, approximately 7 hours before dosing, the run-in period will start with IV infusion of glucose (20% dextrose solution) or insulin (CCI) as needed to reach a target plasma glucose level of 126 (±20) mg/dL (7.0 [±1.1] mM). If this target glucose level is not attained before 11:00 AM, the meal test will be halted and may be performed on a separate inpatient period; each meal test can only be repeated once. During the run-in period, plasma glucose concentrations will be monitored approximately every 30 minutes.

The run-in period will end at approximately 30 minutes before the scheduled start time of the MMTT on Day 1. The MMTT will start in the early morning at approximately 8:00 AM with allowance up to 11:00 AM, if required, to ensure the patient's plasma glucose is stable and at target, with the premeal activities as specified in the Study Schedule (Section 2). LY900014 or Humalog will be given as a bolus dose by a qualified staff member using the insulin pump (time 0) according to the assigned treatment administration mode (Mode 1 or Mode 2) immediately before the start of the test meal. The prandial insulin dose (LY900014 or Humalog) will be 30% greater than the dose calculated from the patients' individual insulin:carbohydrate ratio if the patients' current insulin:carbohydrate ratio does not take into account the necessary dose adaptation for the fat content of the test meal (refer to Section 5.5 for rationale). For each MMTT, the patient should stay in a semi-supine position for 2 hours postdose, and the patient will not be allowed to consume water for 2 hours after dosing.

If a catheter occlusion alarm occurs <5 hours after the start of the MMTT, the data will not be used for analysis, and the MMTT can be repeated a maximum of 1 time. Only data from the repeat MMTT will be used for analysis.

Patients will receive a standardized lunch meal (the same standardized lunch provided on Days 2 and 3) at approximately 1:00 PM and at least 5 hours after the start of the breakfast meal. LY900014 or Humalog bolus dose will be administered by a qualified staff member as a standard or rapid dual-wave bolus using the insulin pump according to the assigned treatment administration mode (Mode 1 or Mode 4) immediately before the start of the lunch meal. The prandial insulin dose (LY900014 or Humalog) will be 30% greater than the dose calculated from

the patients' individual insulin:carbohydrate ratio if the patients' current insulin:carbohydrate ratio does not take into account the necessary dose adaptation for the fat content of the test meal.

Patients will receive a standardized dinner meal (the same standardized dinner provided on Day –1 and Day 2) at approximately 7:00 PM and at least 5 hours after the start of the lunch meal. LY900014 or Humalog will be given as a standard or rapid single-wave bolus dose using the insulin pump according to the assigned treatment administration mode (Mode 2 or Mode 3) immediately before the start of the dinner meal. The prandial insulin dose (LY900014 or Humalog) is individually selected by the patient according to their individually calculated dose and/or insulin:carbohydrate ratio.

5.1.1.3. Day 2 Activities

Patients stay at the CRU overnight and will be tested for plasma glucose approximately every hour during the night (from completion of the Day–1 standardized dinner to 30 minutes before Day 2 dosing) by qualified site staff. If plasma glucose levels fall outside the targeted glucose range (that is, hyperglycemia or hypoglycemia), the site staff will intervene by administering glucose orally or IV, or insulin (CCI) SC or IV up to 6 hours before the start of the planned test meal (approximately 2 AM on Day 2). If the patient requires glucose or insulin treatment during the 6 hours before the meal, the Day 2 high-glycemic test meal will not be performed (test will be handled as missing data). In this case, patients will receive a standardized breakfast (same breakfast as on Days 1 and 3) using a bolus dose selected by the investigator based on the preprandial glucose level and the patients' individual insulin:carbohydrate ratio, but no PK, GD, or other assessments (for example, local tolerability) will be performed. After the overnight fast, the target plasma glucose level before the start of the test meal should be between 71 and 180 mg/dL (3.9 to 10.0 mM). The same reservoir and catheter inserted on Day –1 will be used by the site staff to administer the patient's bolus dose using the CCI with the single-wave, standard or rapid bolus delivery mode as per the randomization schedule before the start of the standardized high-glycemic index breakfast. The patient should stay in a semi-supine position for 2 hours postdose, and the patient will not be allowed to consume water for 2 hours after dosing.

The lunch meal and dinner meal procedures will be performed as described above for the Day 1 procedures.

5.1.1.4. Day 3 Activities

Before the start of the run-in period, the cannulation of 2 veins will be performed. On Day 3, approximately 7 hours before dosing (approximately 1:00 AM), the run-in period for the Day 3 MMTT will start. The run-in period, breakfast MMTT, and lunch meal procedures will be performed as described above for the Day 1 procedures.

If a catheter occlusion alarm occurs <5 hours after the start of the MMTT on Day 3, the data will not be used for analysis and the entire period can be repeated a maximum of 1 time. If catheter occlusion occurs >5 hours after the start of the MMTT on Day 3, the data will be used for analysis for the breakfast meal test, but the lunch test meal on Day 3 will be omitted and handled

as missing data, and the patient will have the catheter and CGM system removed. A new catheter will be inserted for use with the patient's own insulin pump.

After the Day 3 lunch meal procedures are completed (approximately 5 hours after the start of the lunch meal), the catheter and CGM system will be removed. A new catheter will be inserted for use with the patient's own insulin pump. However, if the patient plans to stay at the clinic until that evening (approximately 5:00 PM) for Day –1 procedures for the next period, the new catheter and reservoir will not be inserted until after the standardized dinner (at approximately 7:00 PM) is given (Day –1 for the following period).

Additionally, a macroscopic and microscopic check of the removed catheter and catheter tubing will be performed on site, ideally immediately after removing but within 120 minutes to exclude micro-occlusions and/or particles in the tubing.

5.1.2. Outpatient Procedures

For the time between consecutive periods, patients will continue their CSII therapy with their own pump using Humalog until the evening of Day –1 (after completing the Day –1 standardized dinner) of the next meal test period when they will receive either the LY900014 or Humalog with a CCI [redacted], according to their assigned treatment. Patients will be instructed to perform regular blood glucose monitoring consisting of a minimum of daily 4-point self-measured plasma glucose profiles (preprandial for 3 meals [that is, breakfast, lunch, and dinner] and at bedtime) using their own glucose meters. Patients will be instructed to use a diary to document any AEs, hypoglycemic events, meals (time, units of carbohydrate equivalent), insulin bolus doses and basal rate changes, and the self-measured plasma glucose values. The source data for self-measured plasma glucose values will be the patient's diary. Upon return to the CRU on the evening of Day –1, the diary will be reviewed and checked for hypoglycemic events and AEs. The individual insulin doses may be adapted by the investigator for the outpatient period if clinically indicated to prevent significant hyperglycemia or hypoglycemia. Additionally, as determined by the investigator, interim telephone visits may occur at any time during the outpatient periods to review the safety and well-being of the patient.

5.2. Number of Participants

Initially, 24 patients will be enrolled to target approximately 20 patients to complete all 4 periods of the study. Patients who drop out may be replaced, up to a maximum of 30 total patients enrolled, to ensure 20 completers; the replacement patient will adopt all assigned treatments of the original patient's randomization schedule and complete all 4 study periods.

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

The study is a 4-period crossover design to reduce the variability of insulin PK and GD as each patient will act as his/her own control. On Days 1 and 3, each patient will undergo an insulin

administration using different bolus delivery modes (standard single-wave or standard dual-wave boluses) with LY900014 and Humalog before a solid, individually standardized breakfast test meal (MMTT) is administered; the standard dual-wave mode of administration will be compared to a standard single-wave (traditional) insulin administration via CSII. This design enables the optimization of a bolus delivery for both LY900014 and Humalog by monitoring the PK and GD properties (Luijf et al. 2013). To improve the comparability of the GD effects on Days 1 and 3, an overnight run-in period using a variable insulin and glucose IV infusion has been introduced. This run-in aims to achieve similar preprandial glucose levels for all patients before the start of the test meal and thereby reduces the variability of the postprandial glucose response. Insulin glulisine has been chosen for the IV optimization of plasma glucose during the run-in because insulin glulisine does not cross-react with the insulin lispro–specific assay used for the PK analysis. Because this run-in procedure requires a 7-hour fasting interval before the start of a test meal procedure, the run-in can only be implemented overnight and not for the planned lunch and dinner test meals. The run-in is also not implemented the night before the Day 2 test meal to better mimic the Phase 3 environment in which this meal will be used.

On Day 2, a high–glycemic index breakfast test meal will be administered, comparable to the one chosen for future Phase 3 studies, to test if a rapid or a standard single-wave bolus delivery will have an impact on the postprandial glucose excursions. Since LY900014 is a new formulation of the already marketed short-acting analog, Humalog, the latter is the best comparator to assess potential differences in clinical utility of this novel formulation.

On Days 1, 2, and 3, standardized lunches will be served, and on Days 1 and 2, standardized dinners will be served. The postprandial glucose profiles after these lunches and dinners will be assessed using CGM. For these meals, additional bolus administration options will be tested: standard versus rapid dual-wave bolus administration for lunch test meals and standard versus rapid single-wave bolus administration for dinner test meals. The standardization of the lunch and dinner meals allows the testing of other bolus delivery forms in a controlled environment, and the use of CGM enables the analysis of postprandial glycemic excursions while minimizing the blood loss associated with multiple blood glucose samples.

Under this design, for any 2 consecutive days of a period, the interval between the last bolus on the first day and the first bolus on the second day is much longer compared to the length of time that the treatment (LY900014 or Humalog) lasts in the bloodstream; therefore, no carryover effect is assumed (from Day 1 to Day 2 or from Day 2 to Day 3). This enables PK and GD data from the breakfast meal tests on Days 1 and 3 and Day 2 to be analyzed independently and separately.

5.5. Justification for Dose

The bolus dose of insulin lispro (LY900014 or Humalog) will be individualized per patient to cover the carbohydrate content of both the standardized meals while inpatient at the CRU and meals consumed during the outpatient time period(s) and will be based on the patient's individually calculated dose and/or insulin:carbohydrate ratio; the doses used for the MMTTs (Days 1 and 3) and lunch meals (Days 1, 2, and 3) during the inpatient periods will be

30% greater than the dose calculated from the patient's individual insulin:carbohydrate ratio if the patient's current insulin:carbohydrate ratio does not take into account the necessary dose adaptation for the fat content of the test meal because literature data show that the prandial insulin requirements for MMTTs are 17% to 124% greater for a mixed meal containing a substantial amount of fat compared to a meal with the same carbohydrate content but only a minimal amount of fat (Bell et al. 2016). For each patient, the individualized prandial insulin lispro dose in LY900014 and Humalog for each test meal must be kept identical throughout the crossover periods. The prandial doses of Humalog can be adapted during the outpatient period if clinically indicated.

6. Study Population

Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiograms (ECGs). The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 21 days before the lead-in period. Patients who are not enrolled within 21 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

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

6.1. Inclusion Criteria

Patients are eligible for enrollment in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] are male or female patients with T1DM for at least 1 year. A diagnosis of T1DM is based on medical history with a fasting C-peptide ≤0.30 nmol/L

[1a] male patients: agree to use an effective method of contraception for the duration of the study and for 1 month following the last dose of investigational product

[1b] female patients:

- women of childbearing potential may participate and include those who test negative for pregnancy before initiation of treatment based on a serum pregnancy test and agree to use 1 highly effective method of contraception or a combination of 2 effective methods of contraception during the study and for 1 month following the last dose of the investigational product
- women of nonchildbearing potential may participate in the study without using adequate contraceptive methods and include those who are:
  - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or congenital anomaly such as Müllerian agenesis; or

- postmenopausal, defined as women aged <52 years and being amenorrheic for more than 1 year with a serum follicle-stimulating hormone (FSH) level compatible with postmenopausal status (positive FSH level), or aged ≥52 years and being amenorrheic for <1 year and with a serum FSH level compatible with postmenopausal status or aged ≥52 years being amenorrheic for more than 1 year

[2] are aged between 18 and 70 years, inclusive, at the time of screening

[3] have a body mass index (BMI) ranging from 18.5 to 33.0 kg/m^2 at screening, inclusive

[4] have clinical laboratory test results within normal reference range for the population or investigator site or results with acceptable deviations that are judged to be not clinically significant by the investigator

[5] have a hemoglobin A1c (HbA1c) of <9.0% at screening

[6] have had no episodes of severe hypoglycemia in the past 6 months (severe hypoglycemia is defined as having neurological symptoms consistent with neuroglycopenia and having required assistance in treatment by a second party)

[7] are currently on CSII therapy, with a total insulin dose ≤1.5 U/kg/day and are willing to use a standard pump (CCI [redacted]) and standard catheter and infusion set for the duration of the study

[8] have venous access sufficient to allow for blood sampling and IV infusions as per the protocol

[9] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[10] have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site

6.2. Exclusion Criteria

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

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

[12] are Lilly employees or employees of the investigator site/CRU

[13] are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[14] have participated, within the last 30 days, in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed

[15] are persons who have previously completed or withdrawn from this study

[16] have known allergies to treprostinil (CCI), insulin lispro, CCI , related compounds, or any components of the formulation; or have a history of significant atopy

[17] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[18] have an abnormal blood pressure as determined by the investigator, or results with unacceptable deviations that are judged by the investigator to be clinically significant for the population

[19] have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine (apart from T1DM), hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data

[20] have known slowing of gastric emptying and or gastrointestinal surgery that, in the opinion of the investigator, might change gastrointestinal motility and food absorption

[21] have significant lipohypertrophy in the target abdominal injection area as judged by the investigator

[22] have proliferative retinopathy or maculopathy and/or severe neuropathy; in particular, autonomic neuropathy as judged by the investigator based on a recent (<1.5 years) ophthalmologic examination

[23] have known or ongoing psychiatric disorder(s)

[24] regularly use known drugs of abuse and/or show positive findings on urinary drug screening

[25] show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies

[26] show evidence of hepatitis C and/or positive hepatitis C antibody

[27] show evidence of hepatitis B and/or positive hepatitis B surface antigen

[28] are women who are lactating

[29] have, except for current regimen of insulin therapy and concomitant medication (for example, antihypertensives, lipid-lowering agents), regular use of or intended use of any over-the-counter or prescription medications or nutritional supplements that treat hyperglycemia or insulin resistance or that promote weight loss within 14 days before dosing (apart from vitamin/mineral supplements, ibuprofen, hormone/thyroid-replacement therapy, or hormonal contraceptives)

[30] have intended use of over-the-counter or prescription medications containing acetaminophen (paracetamol) during the study

[31] have regular use of or intended use of known inducers or inhibitors of cytochrome P450 [CYP]2C8 or niacin. Patients taking these medications before study enrollment will be eligible with an appropriate washout period which will be evaluated by the investigator in consultation with the Lilly CRP

[32] had blood loss of more than 500 mL within the last month

[33] have a significant history of alcoholism or drug abuse as judged by the investigator or consuming more than 24 g of alcohol per day for males or more than 12 g of alcohol per day for females or are unwilling to stop alcohol consumption at least 24 hours before each CRU admission (Day –1) and throughout the duration of each CRU visit

[34] are currently a smoker, used tobacco products on a regular basis in the 6 months before screening, or are intending to smoke during the study period

[35] are receiving chronic (lasting longer than 14 consecutive days), systemic, or inhaled glucocorticoid therapy (excluding topical, intra-articular, and intraocular preparations); or have received such therapy within the 4 weeks before screening

[36] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

6.2.1. Additional Exclusion Criteria for Inpatient Dosing Days

Patients who fulfill 1 or more inpatient dosing-day exclusion criteria will be excluded from the MMTT(s) for that treatment period. For each patient, 1 treatment period can be rescheduled 1 to 7 days later. A patient may be replaced if he/she has already missed more than 1 period.

The following exclusion criteria apply to before each inpatient visit:

[37] consumption of alcohol within 24 hours before each of the inpatient periods or a positive result of the alcohol breath test

[38] positive drug screen

[39] positive pregnancy test

[40] consumption of coffee, tea, chocolate, cola, and/or energy drinks containing methylxanthine (caffeine, theophylline, or theobromine) within 12 hours before each test meal

[41] strenuous exercise within 24 hours before each test meal

[42] any medical condition or AE that could interfere with glucose metabolism, as judged by the investigator

[43] any use of prescription or nonprescription medication according to Exclusion Criteria [29] through [31]

[44] hypoglycemia during the treatment period and <24 hours before dosing that poses a significant risk to patient safety, as judged by the investigator

[45] injection of a bolus of more than 6 U of a fast-acting insulin analog between 7 and 12 hours before dosing

[46] change of catheter site during a treatment period from approximately 8 hours before the start of the breakfast meal on Day 1 to approximately 5 hours after the start of the lunch meal on Day 3

6.3. Lifestyle and/or Dietary Requirements

Before beginning the study, the patients will complete an informed consent form (ICF) and screening tests.

Throughout the study, patients may undergo medical assessments and/or a review of compliance with requirements before continuing in the study. Patients should continue to meet the restrictions related to meals, alcohol, tobacco, caffeine, and medication use.

6.3.1. Meals and Dietary Restrictions

While resident in the CRU, patients may not consume any food or caloric drinks other than that provided by the CRU. When not resident in the CRU, patients may resume their regular diet.

6.3.1.1. Mixed-Meal Tolerance Test on Day 1 and Day 3

Patients will be provided individualized breakfast meals for the MMTTs on Day 1 and Day 3, as outlined in the Study Schedule (Section 2). The total caloric content will be approximately 30% of the daily estimated caloric need for weight maintenance. The macronutrient composition of the meals should be targeted to provide approximately 50% of the calories from carbohydrate, 30% of the calories from fat, and 20% of the calories from protein. Patients will be fasted (except for water) for at least 10 hours before each test meal and consume each meal within approximately 20 minutes. Test meals for each patient will be kept consistent with respect to calorie and nutrient content across Day 1 and Day 3 MMTT assessments in the study. The patient will not be allowed to consume water for 2 hours after dosing apart from fluid provided with the meal; however, water may be consumed freely after 2 hours postdose.

The time of meal start and completion, the total calories and grams of carbohydrates consumed in the MMTT, the high-glycemic index meal (Section 6.3.1.2), and the standardized lunch and

dinner meals (Section 6.3.1.3) during the inpatient stays will be captured in the study case report form (CRF).

6.3.1.2. High-Glycemic Index Meal Test on Day 2

In the morning of Day 2 in each period, patients will be provided a high-glycemic index breakfast meal (Section 2) consisting of a solid nutrition bar (such as CCI [redacted]) and a liquid nutrition shake (such as CCI [redacted]) that has a total caloric content of approximately 550 kcal and is expected to be representative of the test meal planned for future Phase 3 studies. The macronutrient composition of the meals should be targeted to provide approximately 50% of the calories from carbohydrate, 30% of the calories from fat, and 20% of the calories from protein. Patients will be fasted (except for water) for at least 10 hours before each test meal and consume each meal within approximately 15 minutes. Test meals for each patient will be kept consistent with respect to calorie and nutrient content across all Day 2 meal test assessments in the study. The patient will not be allowed to consume water for 2 hours after dosing apart from fluid provided with the meal; however, water may be consumed freely after 2 hours postdose.

6.3.1.3. Lunch and Dinner Meals

Patients will be provided individualized standardized lunch meals on Days 1, 2, and 3 and individualized standardized dinner meals on Days 1 and 2, as outlined in the Study Schedule (Section 2). The macronutrient composition of the meals should be targeted to provide approximately 50% of the calories from carbohydrate, 30% of the calories from fat, and 20% of the calories from protein. Patients will consume each meal within approximately 20 minutes. Lunch and dinner meals for each patient will be kept consistent with respect to calorie and nutrient content.

6.3.2. Caffeine, Alcohol, and Tobacco

Patients should refrain from food/beverages containing caffeine (for example, cola, chocolate drinks, tea, coffee, energy drinks containing methylxanthine [caffeine, theophylline, or theobromine]) for at least 12 hours before each CRU admission and throughout the duration of each CRU visit.

No alcohol will be allowed at least 24 hours before each CRU admission (Day –1) and throughout the duration of each CRU visit. Between CRU visits, daily alcohol consumption should not exceed 3 units for males and 2 units for females (a unit is defined in Exclusion Criterion [33], Section 6.2).

No cigarette smoking will be permitted during the study.

6.3.3. Activity

Patients will be encouraged to maintain their regular exercise and insulin regimen adaptation related to exercise during the outpatient period; however, they should not undertake vigorous or prolonged exercise at least 24 hours before each dosing day at the CRU. Movement will be restricted to retain the integrity of connections to infusion(s) and the study procedures.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

7. Treatment

7.1. Treatment Administered

7.1.1. Investigational Medicinal Product

The drug product, LY900014, will be provided as a solution formulation in sterile glass vials. LY900014 is composed of insulin lispro drug substance and the following excipients: sodium citrate, zinc chloride, magnesium chloride, glycerin, m-cresol, and treprostinil. The vial is formulated to deliver 100 units of insulin lispro per milliliter of LY900014.

Humalog administered as a Reference during the inpatient treatment (Periods 1 to 4) will be considered as an investigational medicinal product. Commercially available 10-mL vials will be over-labeled. The vial is formulated to deliver 100 units of insulin lispro per milliliter of Humalog. An unblinded pharmacist at the site will fill the pump reservoirs and attribute them to the respective patients as per randomization schedule.

Both LY900014 and the Reference (Humalog) used during the inpatient periods of the study will be supplied by the sponsor; both will be packaged and labeled for clinical trial use.

7.1.2. Noninvestigational Medicinal Products

For daily dosing during the 1-week lead-in period and between study periods, patients will be provided with commercially available Humalog 10-mL vials for infusion; in these situations, Humalog will be considered as a noninvestigational medicinal product for study procedures. Commercially available CCI) and 20% dextrose will be used for the 7-hour run-in period before the start of the MMTTs on Days 1 and 3 and can be used up to approximately 6 hours before the start of the Day 2 breakfast test meal. In addition, if a patient's plasma glucose concentration rises above 306 mg/dL (17 mM) for more than 1 hour during the meal test, CCI will be administered. Apidra or IV glucose can also be administered during the complete inpatient period outside of the test meal procedures if required to treat hypo- or hyperglycemia at the discretion of the investigator.

The doses of Humalog, CCI , and glucose administered during the trial must be recorded in the CRF.

Humalog used as a noninvestigational medicinal product will be supplied by the sponsor. All other noninvestigational medicinal products will be sourced locally by the site and will be used from their original packaging.

7.1.3. Inpatient Dosing

During inpatient stays (Day –1, starting after the administration of the standardized dinner, to Day 3), all study drug will be administered with a CCI . A standardized catheter with a 6-mm needle length will be inserted on the day before the first meal test is administered (Day –1) during each period, and the catheter site must remain the same until the lunch meal procedures on Day 3 have been completed. Catheter insertion sites selected should be in the abdominal area, and the treatment will be administered SC. Catheter insertions

should be performed by a limited number of qualified and appropriately trained site personnel as designated by the investigator for consistency.

The insulin pump reservoir will be filled with either LY900014 or Humalog by qualified site staff while maintaining the blind for the investigator and patient.

Unless the patient decides to stay in the CRU for the next study period, after each period, the CCI will be changed to the patient's own personal pump and the catheter will be changed.

7.1.4. Outpatient Dosing

For the time between consecutive periods, patients will continue their CSII therapy with their personal pump using Humalog until the evening of Day –1 (after administration of the standardized dinner) of the next meal test period when they will receive either the LY900014 or Humalog, according to their assigned treatment.

Patients will be asked to record the date, time, and dosages of prandial and basal Humalog doses in a patient diary between study periods.

7.1.5. Packaging and Labeling

LY900014 will be supplied by Lilly or its representative in accordance with current good manufacturing practices and will be supplied with lot numbers. Reference drug will be commercially available insulin lispro (Humalog U-100) supplied by Lilly.

The study insulins will be provided to the site unblinded. The glass vials will each contain 10 mL of either LY900014 or Humalog with an insulin lispro concentration of 100 U/mL. An unblinded pharmacist at the site or other site personnel who are unblinded will use the insulin vials provided to prepare the blinded vials.

7.2. Method of Treatment Assignment

Each patient will be randomized to 1 of 4 treatment sequences (4 periods per sequence) comprising of LY900014 or Humalog, administered as a CSII with different bolus administration modes, determined according to a randomization schedule.

7.2.1. Selection and Timing of Doses

For each meal test, the doses will be administered at time "0," immediately before the start of a test meal. The test meal will be given at approximately the same time on Days 1, 2, and 3 of each study period. Specific patient restrictions are described in Section 6.3. The actual time of all dose and test meal administrations will be recorded in the patient's CRF.

7.3. Blinding

This is a patient- and investigator-blind study. Blinding will be maintained throughout the conduct of the trial until all data are cleaned to an acceptable level of quality and locked. The details are included in the blinding/unblinding plan.

To preserve the blinding of the study, only a minimum number of personnel at the site will see the randomization table and codes before the study is complete.

Emergency codes will be available to the CRU. A code, which reveals the treatment group for a specific study patient, may be opened during the study only if the patient's well-being requires knowledge of the patient's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. 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 pharmacologist or CRP before unblinding a study patient's treatment assignment unless this could delay emergency treatment of the patient. If a study patient's treatment assignment is unblinded, Lilly must be notified immediately.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

For the inpatient period, there will be no dose modifications of LY900014 for the meal tests and basal rates unless medically indicated and confirmed between the sponsor CRP and the investigator.

For the outpatient period, the individual insulin doses may be adapted by the investigator if clinically indicated to prevent significant hyperglycemia or hypoglycemia.

7.5. Preparation/Handling/Storage/Accountability

LY900014 and Humalog will be provided to the site by the sponsor.

Patients will be supplied with a standard infusion set at the lead-in visit.

The investigator or designee is responsible for:

- explaining the correct use of the investigational agents to the site personnel;
- verifying that instructions are followed properly;
- maintaining accurate records of investigational product dispensing and collection; and
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

All clinical study material provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the

investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained. The investigator site will be permitted to destroy the investigational material after written approval is obtained from the sponsor and must retain appropriate documentation for the destruction of the material.

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

Every attempt will be made to select patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the study site.

The specifications in this protocol for the timings of safety (including pain and insertion-site assessments), PK, and GD sampling are given as targets, to be achieved within the time windows described in the study-specific CRF completion guidelines. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure to obtain samples and perform protocol-specific procedures outside the allowable time window because of clinical issues, such as problems with venous access, technical problems with equipment, or problems with patient no-show for scheduled procedures, will not be considered a protocol deviation but the site will still be required to notify the sponsor in writing. Written documentation (for example, a note-to-file) will have to be provided to the sponsor for all missing or delayed samples and procedures (regardless of reasons) to facilitate data reconciliation before study completion.

Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

7.7. Concomitant Therapy

Patients on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. Patients will continue their basal insulin infusion rate during the entire study except when presenting safety issues and during the breakfast test meal period as defined in Section 5.1; in case of safety-driven indications for a basal-rate adaptation, the investigator will discuss a change of the regimen of insulin basal rate to prevent any medical problems. Any change in the basal rate will be captured in the patient diary and CRF.

Patients should not use over-the-counter or prescription medication (other than their current regimen of insulin therapy and concomitant medication [for example, antihypertensives, lipid-lowering agents] at enrollment) or nutritional supplements that affect blood glucose or the body's sensitivity to insulin or that promote weight loss 14 days before dosing (apart from

vitamin/mineral supplements, ibuprofen, hormone/thyroid-replacement therapy, or hormonal contraceptives) or throughout the study (refer to Section 6.2). Drugs or supplements that are known inducers or inhibitors of CYP2C8 are not permitted as they may alter the PK of treprostinil.

Patients should not use over-the-counter or prescription medications containing acetaminophen (paracetamol) because it is known to interfere with CGM sensing, resulting in falsely elevated CGM glucose values.

Patients should not apply any creams or lotions to the abdominal skin on the morning of the catheter insertion or during the inpatient study procedure.

If the need for concomitant medication arises (for example, to treat an AE or infusion-site pain), inclusion or continuation of the patient may be at the discretion of the investigator, preferably after consultation with a Lilly clinical pharmacologist or CRP. Any additional medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

LY900014 will not be made available to subjects after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product 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:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5X upper limit of normal (ULN)
- ALT or AST >3X ULN along with one of the following criteria
    - sustained for more than 2 weeks or
    - total bilirubin level >2X ULN or
    - prothrombin time >1.5X ULN or
    - 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 total bilirubin level >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 who discontinue the investigational product early will have procedures performed as shown in the Schedule of Activities (Section 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, a discussion must occur between the Lilly clinical pharmacologist/CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist/CRP to allow the inadvertently enrolled patient to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision

  - the investigator decides that the patient should be discontinued from the study
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs before introduction of the new agent

- subject decision
  - the patient or designee (for example, parents or legal guardian) requests to be withdrawn from the study

Patients who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Patients 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.

9. Study Assessments and Procedures

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

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

Appendix 4 provides a summary of the maximum number and volume of invasive samples for all sampling during the study.

Unless otherwise stated in 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.

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important; that are considered related to the investigational product, the Humalog noninvestigational product, or the study; or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed 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.

After the ICF is signed, study site personnel will record, via the CRF, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment 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 investigational product and/or study procedure and the AE.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via the CRF.

9.2.1. Serious Adverse Events

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

- 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
- events considered significant by the investigator based upon appropriate medical judgment

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.

Although all AEs are recorded in the CRF after signing informed consent, SAE reporting begins after the patient has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent but before receiving investigational product AND is considered Reasonably Possibly Related to a study procedure, then it MUST be reported.

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

Pregnancy (maternal or paternal exposure to investigational product) 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.

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 investigational product or procedure. US 21 CFR 312.32 and EU Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of

SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Excess insulin administration may cause hypoglycemia. For the purposes of this study, an overdose of LY900014 is considered any dose higher than the calculated individualized dose to cover the carbohydrate content of meals consumed during the study.

Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/SC glucagon or concentrated IV glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

Refer to the IB for LY900014 and the package insert for insulin lispro (Humalog package insert 2015).

9.4. Safety

9.4.1. Laboratory Tests

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

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Routine clinical laboratory tests will be analyzed by a local laboratory.

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2) and as clinically indicated.

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

If orthostatic measurements are required, patients should be supine for at least 5 minutes and stand for at least 2 minutes.

If the patient feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted and agreed upon between the sponsor and investigator.

Body temperature will be measured as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.3. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.4. Body Weight

Body weight will be recorded as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.5. Electrocardiograms

For each patient, single 12-lead digital ECGs will be collected according to the Schedule of Activities (Section 2). ECGs must be recorded before collecting any blood for safety or PK tests. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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

If a clinically significant finding is identified (including, but not limited to, changes in QT/QT corrected for heart rate [QTc] interval from baseline) after enrollment, the investigator will determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.6. Plasma Glucose Monitoring

The patient's plasma glucose concentrations will be monitored frequently at the times specified in the Schedule of Activities (Section 2) using a CCI [redacted] available at the site for safety assessments.

Additionally, patients will be instructed to conduct daily self-plasma glucose monitoring at a minimum of 4 time points (premeals: breakfast, lunch, dinner; and bedtime) during the outpatient phase of the study. Patients will be instructed to immediately report any episodes of hyperglycemia or hypoglycemia requiring an adaptation of the treatment regimen to the investigator, who will be responsible for advising the patient on what further actions to take.

Patients will be instructed to record the date, time, and result of each self-plasma glucose monitoring test. Additional monitoring may be requested at the investigator's discretion.

Hypoglycemic episodes will be defined as clinical events with or without symptoms typical of hypoglycemia, accompanied by a plasma glucose level of ≤70 mg/dL (3.9 mM), which are reversed by oral carbohydrates or IV glucose. These episodes will be captured in the CRF. In addition, episodes that fulfill the criteria of severe hypoglycemia as defined in Section 9.4.9.1 will be reported as an SAE. Investigator review of glucose results clinically indicative of hypoglycemia will be required.

Hypoglycemia is considered a therapeutic effect of insulin lispro and will generally not be considered a clinically significant drug-related AE but will be treated appropriately. Additional monitoring of plasma glucose levels may be performed at the discretion of the investigator.

9.4.7. Catheter Insertion-Site Assessments

Catheter insertion-site assessments, including inspection of the site for signs such as edema, erythema, and rash, will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.7.1. Subjective Procedure: Examination of Infusion Set and Catheter

When the infusion set and reservoir are changed (except for Period 1, Day –1) at the site, a macroscopic (visual) and microscopic examination (ideally immediately after removing the catheter, but no longer than 120 minutes) will be performed including the following:

- a check on the infusion set or the catheter for signs of kinking or other damage. In case of damage, the damage should be described in the CRF and photographic evidence should be taken
- a check of the insulin in the reservoir and infusion-set tubing for color change and crystals and/or particles including the location of these (that is, reservoir, infusion set)
- a microscopic check of the catheter tubing to exclude micro-occlusions and/or particles in the tubing

9.4.7.2. Subjective Procedure: Acceptability of Insulin Delivery Experience

Subjects will be asked to provide the acceptability of their overall experience with the study insulin delivery via the CCI [redacted] at the end of each study period, prior to discharge from the CRU. If the subject plans to stay on after Day 3 and continue on to Day -1 activities for the next period, the assessment will be performed after the Day 3 lunch meal procedures are completed (approximately 5 hours after the start of the lunch meal).

9.4.8. Pain Measurements Using the Visual Analog Scale

Pain measurements during bolus application will be assessed using the electronic version of the 100-mm validated VAS (or electronic VAS [eVAS]) for pain. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess catheter insertion-site pain. The eVAS (van Duinen et al. 2008) is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "no pain" and "worst imaginable pain." The patient is asked to mark the 100-mm line electronically

to indicate pain intensity. The patient will be asked to rate any pain associated during each inpatient infusion on a scale of 0 to 100 mm immediately (within 1 minute) following the start of the infusion and will be asked to rate the pain at the catheter insertion site at time points according to the Schedule of Activities (Section 2) and as clinically indicated.

As catheter insertion-site pain is an expected AE, insertion-site pain (especially transient episodes of pain) will generally not be considered a clinically significant event unless the duration or intensity of the pain interferes with normal activities of daily living or constitutes a risk to the well-being of the patient. Analgesia can be prescribed in response to pain and must be documented in the concomitant medication section of the CRF.

9.4.9. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate and periodically review:

- trends in safety data
- laboratory analytes
- AEs

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated total bilirubin ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend on the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and compliance with regulatory guidance, the investigator is to consult with the Lilly designated CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (Appendix 4).

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the unblinding/blinding plan.

9.4.9.1. Glucose Monitoring

Hypoglycemia will be described using the following definitions:

- Documented hypoglycemia:
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by plasma glucose ≤70 mg/dL (3.9 mM)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with plasma glucose ≤70 mg/dL (3.9 mM)

- **Unspecified hypoglycemia**: an event during which plasma glucose ≤70 mg/dL (3.9 mM) but no information relative to symptoms of hypoglycemia was recorded
- **Probable symptomatic hypoglycemia:** an event during which symptoms indicative of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by plasma glucose ≤70 mg/dL [3.9 mM])
- **Severe hypoglycemia:** an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status and cannot assist in their own care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (≤70 mg/dL [3.9 mM])
- **Nocturnal hypoglycemia:** any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking
- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, that do not require the assistance of another person, are accompanied by plasma glucose >70 mg/dL (3.9 mM), but these levels may be quickly approaching the 70-mg/dL (3.9 mM) threshold
- **Total hypoglycemia:** an optional category that combines all cases of hypoglycemia. If an event which hypoglycemia falls into multiple subcategories, the event is only counted once in this category

Investigator review of documented glucose results in the diary or during the inpatient period that are clinically indicative of hypoglycemia will be required.

9.4.10. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro at the times specified in the Schedule of Activities (Section 2). Additional samples may be collected if there is a possibility that an AE is immunologically mediated. Immunogenicity will be assessed using a validated radioligand-binding assay designed to detect anti-insulin lispro antibodies and characterize cross-reactivity to insulin.

Since the characterization of insulin antibodies is readily available, reliable on-market data exists showing that anti-insulin antibodies, while present, do not appear to be clinically consequential (Fineberg et al. 2003), and in vivo measures exist to allow for identification of those patients who may lose efficacy to insulin lispro; Lilly intends to use these measures (that is, HbA1c and serum glucose) as direct measures of a neutralizing effect.

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

9.5. Pharmacokinetics

Venous blood samples of approximately 1 mL each will be collected to determine the serum concentrations of insulin lispro at the visits and times specified in the Schedule of Activities (Section 2). The actual date and time (24-hour clock time) of each sampling will be recorded.

The time points for insulin lispro blood sampling may be modified during the study if warranted and agreed upon between both the investigator and sponsor, but no additional samples will be drawn. Instructions for the collection and handling of blood samples will be provided by the sponsor.

Drug concentration information that would unblind the study will not be reported to the investigative site or blinded personnel until the study has been unblinded.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Serum samples will be analyzed for insulin lispro concentrations using a validated enzyme-linked immunosorbent assay (ELISA) that is specific for insulin lispro. Samples remaining after the bioanalyses may be used for exploratory analyses.

Bioanalytical samples collected to measure insulin lispro concentrations will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Blood samples (approximately 0.2 mL each) will be collected for the measurement of plasma glucose at the times specified in the Schedule of Activities (Section 2) using a validated method (for example, CCI [redacted]) that will be readily available at the investigative site during the inpatient periods in order to provide real-time glucose measurement. Repeat samples for counterchecking of apparent spurious results may be taken when indicated.

The samples will be discarded after analysis and/or confirmation of results.

9.6.1. Glucose Samples (Inpatient Periods)

Plasma glucose concentrations will be monitored approximately every 30 minutes during the run-in period on Days 1 and 3 (approximately 7 hours before dosing) for the MMTTs.

Plasma glucose concentrations will be monitored approximately every hour during the night on Day 2 (approximately 6 hours before dosing) for the high-glycemic index meal test.

Regular monitoring of blood glucose using the CCI [redacted] (approximately every 2 hours) will also be performed during the complete inpatient period outside of the breakfast

meal test procedures and includes predose before the standardized lunch and dinner as well as for the calibration of the CGM system.

9.6.2. Glucose Samples (Mixed-Meal Tolerance Test)

Blood samples will be obtained for the measurement of plasma glucose concentrations (CCI [redacted]) at the times specified in the Schedule of Activities (Section 2). These glucose measurements will be used for patient safety management (Section 9.4.6) as well as for GD evaluations.

9.6.3. Exploratory Continuous Glucose Monitoring

For the CGM, a standard system (for example, the CCI [redacted]) will be used in a blinded mode (that is, patients will not be able to see their glucose values). The CGM sensor will be inserted by qualified site personnel, and the patients will be instructed to always carry the receiver with them. The CGM device will be calibrated using the plasma glucose values obtained with the CCI [redacted] by qualified site personnel. The patients will wear this device from approximately 12 hours before the start of the breakfast meal on Day 1 to approximately 5 hours after the start of the lunch meal on Day 3 for each inpatient period. The monitor will record continuous glucose measurements. At the end of the recording, the CGM sensor will be removed, and the receiver will be used to download the glucose data.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to the investigational product and to investigate genetic variants thought to play a role in the disease under investigation in this study. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit or for a shorter period if local regulations and/or ERBs impose shorter time limits for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY900014 or after LY900014 is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

An initial 24 patients may be randomized in order that approximately 20 patients complete the study. Twenty completing patients will provide approximately 80% power to demonstrate a 25% decrease in the time to early half-maximal concentration (early 50% T_{max}) between LY900014 and Humalog. Testing will be done at an α-level of 0.1 with a 2-sided confidence interval (CI). The variability was estimated by analyzing internal Lilly data (CCI [redacted]) for LY900014 and Humalog administered on CSII therapy, resulting in approximately 35.9% coefficient of variation of within-subject variability for early 50% T_{max}.

Patients who are randomized but drop out before completing assigned treatment may be replaced to ensure that approximately 20 patients complete the study (refer to Section 5.1).

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

The patient's disposition will be recorded. All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.2.2. Study Participant Characteristics

The patient's age, sex, weight, BMI, height, race/subrace, smoking habits, and other demographic characteristics will be recorded.

10.3. Statistical Analyses

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

Primary statistical analyses will be conducted on the set of patients receiving at least 1 dose of the study drug to which they are randomized. The populations for the PK or GD analyses are defined in more detail in Section 10.3.2.1 and Section 10.3.3.1, respectively. Supportive analyses will be conducted on the set of patients who complete the study according to the sequence/treatment to which they are randomized. Safety analyses will be conducted on the set of patients receiving at least 1 dose of the study drug to which they are randomized and have at least 1 postdose safety assessment, regardless of whether or not they complete all protocol requirements.

For all PK/GD analyses (only applicable for breakfast meal tests), Days 1 and 3 and Day 2 will be analyzed using 2 separate and independent statistical models, assuming no carryover effect of the bolus administration mode from Day 1 to Day 2 or from Day 2 to Day 3 (refer to Section 5.4).

The CGM analyses for lunch and dinner will be documented in the statistical analysis plan.

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 study results.

Additional exploratory analyses of the data may be conducted as deemed appropriate. Analyses will be fully detailed in the statistical analysis plan. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with posthoc analyses and incomplete disclosures of analyses. Analyses will be fully detailed in the clinical study report, synopsis, and/or manuscript.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All treatment- (investigational product and Humalog noninvestigational product) and procedure-related AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur before study enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Patients who complete at least 1 MMTT and have measurable insulin lispro concentrations will be included in the analysis dataset for the PK analyses. Patients who did not keep identical insulin lispro doses for the MMTTs (Days 1 and 3) will be excluded from the PK analysis on the MMTT days. In addition, patients who did not keep identical insulin lispro doses for the high-glycemic index meal tests (Day 2) will be excluded from the PK analysis on the Day 2 meal test days.

PK analyses will be conducted using standard noncompartmental methods of analysis on a computer that meets or exceeds the minimum system requirements for these programs. It is possible that other validated equivalent PK software programs may be used if appropriate, warranted, and approved by global PK management. The version of any software used for the

analysis will be documented, and the program will meet the Lilly requirements of software validation.

Serum insulin lispro concentrations will be used to calculate several PK parameters, including time to maximum concentration (T_{max}), early 50% T_{max}, time to late half-maximal concentration (late 50% T_{max}), C_{max}, area under the plasma concentration versus time curve (AUC) from time 0 to 15 minutes postdose (AUC[0-15min]), AUC from time 0 to 30 minutes postdose (AUC[0-30min]), AUC from time 0 to 1 hour postdose (AUC[0-1h]), AUC from time 0 to the last recorded time (AUC[0-t_{last}]), and AUC from time 0 to 5 hours postdose (AUC[0-5h]). These will be the key parameters for analysis; other parameters (that is, partial AUCs) may be calculated as deemed appropriate.

Although attempts will be made to adhere to the scheduled collection times (Section 2), it is recognized that situations arise that may compromise sample collection at the scheduled times. Parameters will be individually calculated for each patient based on actual collection times and presented by summary statistics**.**

10.3.2.2. Pharmacokinetic Statistical Inference

Log-transformed insulin lispro T_{max}, early 50% T_{max}, late 50% T_{max}, C_{max}, and AUC estimates will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog, and the corresponding 90% CIs of the ratios.

The statistical model for the Day 1 and Day 3 breakfast meal tests will include treatment (4 combinations of treatment and bolus administration mode: LY900014 dual-wave, Humalog dual-wave, LY900014 single-wave, or Humalog single-wave), period, day-within-period, and treatment-by-day-within-period interaction as fixed effects and patient as a random effect. A separate analysis model will be used for the Day 2 breakfast meal test, including treatment (4 combinations of treatment and bolus administration mode: LY900014 rapid, LY900014 standard, Humalog rapid, or Humalog standard, all given as a single-wave bolus) and period as fixed effects and patient as a random effect. The variance-covariance structure considerations will be detailed in the statistical analysis plan. For the primary inference, insulin lispro administered from LY900014 will be concluded to have a significantly decreased early 50% T_{max} relative to Humalog if the upper confidence bound of the 2-sided 90% CI of the ratio of geometric means of the early 50% T_{max} is <1.

As a sensitivity analysis, early 50% T_{max} will be analyzed using the Wilcoxon signed-rank test. The difference in median early 50% T_{max} between LY900014 and Humalog and the 90% CIs for the difference will be presented.

10.3.3. Glucodynamic Analyses

10.3.3.1. Glucodynamic Parameter Estimation

Patients who receive at least 1 dose of study drug and have evaluable GD data will be included in the analysis set for the GD analyses. Also, for Days 1 and 3 and Day 2, separately, patients who did not complete the entire test meal or had significant changes in nutrient consumption of the

test meal or dose changes during the breakfast test meal will be excluded from all the GD analyses.

Data will be analyzed for the patients during each MMTT. The change from baseline values (the average of -30, -15, and 0 minutes represented as the 0-hour time point) for each patient will be calculated. Incremental change from baseline glucose AUC values will be calculated during a 5-hour meal test. Partial AUCs may be calculated as deemed appropriate.

10.3.3.2. Glucodynamic Statistical Inference

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented by treatment and by bolus dose administration mode (all 4 combinations of treatment) for Days 1 and 3 and Day 2, separately. The same statistical model and comparisons used to analyze the PK parameters will be used to analyze the GD parameters on the original scale (not log-transformed) using Fieller's theorem (Chow and Liu 2009).

10.3.4. Exploratory Continuous Glucose Monitoring Analyses

The CGM outcome variables (for example, incremental change from baseline AUC[0-5h], the change from baseline 1- and 2-hour excursions) will be derived based on the raw data collected from the individualized standardized lunch meals on Days 1, 2, and 3 and from the individualized standardized dinner meals on Days 1 and 2. These will be the key parameters for analysis; other parameters (for example, partial AUCs) may be calculated as deemed appropriate. The CGM analysis details will be documented in the statistical analysis plan.

10.3.5. Evaluation of Immunogenicity

The relationship between the status (positive or negative) of treatment-emergent anti-insulin lispro antibodies and TEAEs will be assessed. Likewise, the relationship between the status of treatment-emergent antibodies and the PK parameters and GD response to insulin lispro may also be assessed.

10.3.6. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

The Lilly clinical pharmacologist/CRP/Lilly study team is unblinded. Data may be accessed and analyzed while the trial is ongoing, but no changes to the study design are planned. The results may help Lilly expedite final delivery and enable planning of future studies. Information that may unblind the study during the analyses will not be reported to the study site until the study has been unblinded. An assessment committee will not be formed.

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation subject 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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-15min)	AUC from time 0 to 15 minutes postdose
AUC(0-30min)	AUC from time 0 to 30 minutes postdose
AUC(0-1h)	AUC from time 0 to 1 hour postdose
AUC(0-5h)	AUC from time 0 to 5 hours postdose
AUC(0-t_{last})	AUC from time 0 to the last recorded time
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind trial 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 trial is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences

C_{max}	maximum concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF	case report form: Sometimes referred to as clinical report form. A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	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.
CRU	clinical research unit
CSII	continuous subcutaneous insulin infusion
CYP	cytochrome P450
early 50% T_{max}	time to early half-maximal concentration
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
end of study (trial)	End of study is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last patient.
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: A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical trial are protected.
eVAS	electronic visual analog scale
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

GCP	good clinical practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial patients are protected.
GD	glucodynamic(s)
GRAS	Generally Recognized as Safe
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
ICF	informed consent form: A Lilly term used to describe (1) information regarding the trial for the subject/patient, and (2) the document that the subject/patient signs to indicate consent to participate in the clinical trial.
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	investigational medicinal product
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous
late 50% T_{max}	time to late half-maximal concentration
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial.
MDI	multiple daily injections
MMTT	mixed-meal tolerance test

noninvestigational product	A product that is not being tested or used as a reference in the clinical trial, but is provided to patients and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
PAH	pulmonary arterial hypertension
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PK	pharmacokinetic(s)
randomize	The process of assigning subjects to an experimental group according to the randomization schedule for the trial.
rescreen	To screen a patient who was previously declared a screen failure for the same study.
SAE	serious adverse event: Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this trial, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment.
T_{max}	time to maximum concentration
ULN	upper limit of normal
URI	ultra-rapid insulin
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]	Clinical Chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Glucose (fasting)
Absolute counts of:	Blood urea nitrogen (BUN)
Neutrophils	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
Platelets	Alkaline phosphatase
HbA1c[b]	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis[a]	Creatinine
Specific gravity	Gamma-glutamyl transferase (GGT)
pH	C-peptide[b] (fasting)
Protein	
Glucose	Serology
Ketones	Hepatitis B surface antigen[b]
Bilirubin	Hepatitis C antibody[b]
Urobilinogen	HIV[b]
Nitrite	
Erythrocytes/hemoglobin	Pregnancy test[d]
Leucocytes	Urine drug screen[e,f]
Microscopy[c]	Follicle-stimulating hormone[b]
Coagulation[b]	
International normalized ratio (INR)	
Partial thromboplastin time (PTT)	

Abbreviations: HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

a Results will be validated by the local laboratory at the time of initial testing.

b Performed at screening only. Hepatitis B and HIV tests may be waived if they have been performed within the 6 months before screening (with reports available for review).

c If clinically indicated, per investigator's discretion.

d Females only: serum pregnancy test at screening; urine pregnancy test for all other visits.

e Urine drug screen may be repeated before any admission to the clinical research unit.

f Urine drug screen: amphetamine, cannabis, cocaine, barbiturates, methadone, benzodiazepines, tricyclic antidepressants, methamphetamine, opiates, and phencyclidine.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- 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) before the performance of any protocol procedures and before 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 trial

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council on 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. Lilly or its representatives must approve the ICF before it is used at the investigative site. All ICFs must be compliant with the ICH guideline on good clinical practice (GCP).

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

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

Regulatory Considerations

This study will be conducted in accordance with:

1) 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

2) applicable ICH GCP guidelines

3) applicable laws and regulations

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

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.

Final Report Signature

The investigator or designee will sign the clinical study report for this study indicating agreement with the analyses, results, and conclusions of the report.

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

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
- provide 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 the 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/or 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 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 the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with 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
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
CPK	

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

a Assayed by a Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I8B-MC-ITSC Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	12	1	12
Clinical laboratory tests[a]	9	2	18
Pharmacokinetics (insulin lispro)	1.0	21 x 3 MMTT days x 4 periods	252
Blood for glucose[a]	0.2	24 x 3 MMTT days x 4 periods	57.6
Sample for immunogenicity	5	2	10
Pharmacogenetics	10	1	10
Blood for glucose during run-in period for Days 1 and 3 only (30-minute interval sampling)	0.2	14 x 2 MMTT days x 4 periods	22.4
Blood for glucose before Day 2 meal test	0.2	12 x 4 periods	9.6
Blood for glucose every 2 hours during inpatient and predose for lunch and dinner meals and CGM calibration	0.2	(2 [CGM calibration] plus 5 [premeal] plus 33 [every 2 hours]) x 4 periods	32
Total			423.6
Total for clinical purposes (rounded up to nearest 10 mL)			**430**

[a] Additional samples may be drawn if needed for safety purposes.

Appendix 6. Protocol Amendment I8B-MC-ITSC(a) Summary [A Study to Assess the Pharmacokinetics, Glucodynamics, Safety, and Tolerability of LY900014 in Patients with Type 1 Diabetes Mellitus on Continuous Subcutaneous Insulin Infusion Therapy]

Protocol I8B-MC-ITSC, A Study to Assess the Pharmacokinetics, Glucodynamics, Safety, and Tolerability of LY900014 in Patients with Type 1 Diabetes Mellitus on Continuous Subcutaneous Insulin Infusion Therapy, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Removed reference to a separate manual for instructions to the site for examination of the infusion set and catheter, as these details have been included in the Protocol (Section 9.4.7.1), and hence no longer required.
- Added a subject assessment procedure to enable the site to collect overall acceptability of insulin delivery experience for each study period.
- Corrected minor formatting and grammatical inconsistencies and updated the full name of ICH (“Conference” to “Council”) although these had not been put in tracked changes.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITSC

Procedure	…	…	…	…	…	Day 3	…	Comment
…	…	…	…	…	…	…	…	
Assessment of insulin delivery experience						X		Subjects will be asked to provide the overall acceptability of their insulin delivery experience, either prior to CRU discharge or after completing Day 3 lunch procedures for each period.
…	…	…	…	…	…	…	…	

5.1.1.4. Day 3 Activities

Additionally, a macroscopic and microscopic check of the removed catheter and catheter tubing will be performed on site, ideally immediately after removing but within 120 minutes to exclude micro-occlusions and/or particles in the tubing ~~according to instructions provided to the site in a separate manual~~.

9.4.7.1. Subjective Procedure: Examination of Infusion Set and Catheter

When the infusion set and reservoir are changed (except for Period 1, Day –1) at the site, a macroscopic (visual) and microscopic examination (ideally immediately after removing the catheter, but no longer than 120 minutes) will be performed ~~(according to instructions provided to the site in a separate manual)~~ including the following:

- a check on the infusion set or the catheter for signs of kinking or other damage. In case of damage, the damage should be described in the CRF and photographic evidence should be taken
- a check of the insulin in the reservoir and infusion-set tubing for color change and crystals and/or particles including the location of these (that is, reservoir, infusion set)
- a microscopic check of the catheter tubing to exclude micro-occlusions and/or particles in the tubing

9.4.7.2. Subjective Procedure: Acceptability of Insulin Delivery Experience

Subjects will be asked to provide the acceptability of their overall experience with the study insulin delivery via the [redacted] at the end of each study period, prior to discharge from the CRU. If the subject plans to stay on after Day 3 and continue on to Day -1 activities for the next period, the assessment will be performed after the Day 3 lunch meal procedures are completed (approximately 5 hours after the start of the lunch meal).