Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro (Humalog) Following Single Dose Administration in Japanese Patients With Type 1 Diabetes Mellitus

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Protocol I8B-MC-ITRZ
Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro (Humalog) Following Single Dose Administration in Japanese Patients with Type 1 Diabetes Mellitus

LY900014

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1. Protocol Synopsis

Title of Study:
Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro (Humalog) Following Single Dose Administration in Japanese Patients with Type 1 Diabetes Mellitus

Rationale:
LY900014 is an ultra-rapid-acting insulin lispro formulation with increased early absorption compared to commercially available insulin lispro formulation (Humalog®, Eli Lilly and Company). LY900014 aims to closely mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions better than the currently available treatments.

The previous study with LY900014 in Japanese healthy subjects used an extemporaneous preparation. The aim of this study is to compare the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) profiles of the proposed LY900014 commercial formulation administered from prefilled pens with those of insulin lispro (Humalog) during a euglycemic clamp in Japanese patients with type 1 diabetes mellitus (T1DM).

Objectives/Endpoints:

Objectives	Endpoints
Primary To compare the PK of insulin lispro following administration of a single 15-U SC dose of LY900014 to insulin lispro (Humalog) in Japanese patients with T1DM.	Early 50% t_{max} and $AUC_{(0\text{-}30min)}$
Secondary • To compare the GD during a euglycemic clamp following administration of a single 15-U SC dose of LY900014 or insulin lispro (Humalog) in Japanese patients with T1DM. • To evaluate the safety and tolerability of the proposed commercial formulation of LY900014.	• Early 50% TR_{max}, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1h)}$, and T_{onset} • AEs

Abbreviations: AE = adverse event; $AUC_{(0\text{-}30min)}$ = area under the concentration versus time curve from time zero to 30 minutes; early 50% t_{max} = time to early half-maximal serum concentration; early 50% TR_{max} = time to early half-maximal glucose infusion rate before time to maximum glucose infusion rate; GD = glucodynamic; $Gtot_{(0\text{-}30min)}$ = total amount of glucose infused over 30 minutes; $Gtot_{(0\text{-}1h)}$ = total amount of glucose infused over 1 hour; PK = pharmacokinetics; SC = subcutaneous; T1DM = type 1 diabetes mellitus; T_{onset} = time to onset of insulin action.

Summary of Study Design:
Study I8B-MC-ITRZ is a single center, randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study in Japanese patients with T1DM.

Treatment Arms and Planned Duration for an Individual Patient:
Patients will be randomized to 1 of 2 treatment sequences. The study includes up to a 28-day screening period, 2 treatment periods (2 days inpatient for each period) with 3 to 28 days washout between Periods 1 and 2, and a follow-up period at least 14 days after last dose.

LY900014: Single 15-U subcutaneous (SC) dose

Insulin lispro (Humalog): Single 15-U SC dose

Number of Patients:
Up to 40 patients may be enrolled in order that approximately 28 patients complete the study.

Statistical Analysis:

The primary statistical analyses for PK will be conducted on patients who receive at least 1 dose of study drug and have measurable and evaluable insulin lispro concentrations. The primary statistical analysis for GD will be conducted on those patients who complete at least 1 clamp procedure and have evaluable GD parameters. Supportive analyses will be done on the key parameters for the patients who complete all treatment periods with evaluable data. Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

Safety: All investigational product and protocol procedure adverse events will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety parameters that will be assessed include safety laboratory parameters, vital signs, and electrocardiogram parameters as well as injection-site reactions. The parameters will be listed and summarized using standard descriptive statistics.

Pharmacokinetics: Patients who receive at least 1 dose of study drug and have measurable insulin lispro concentrations will be included in the PK analysis dataset. The PK parameter estimates for insulin lispro will be calculated using standard noncompartmental methods of analysis.

Log-transformed maximum observed concentration (C_{max}) and area under the concentration versus time curve (AUC) for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog, and their corresponding 95% confidence intervals (CIs) using the mixed-effects model that includes treatment, sequence, and period as fixed effects and patient within sequence as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters: time to early half-maximal serum concentration (early 50% t_{max}), time to late half-maximal serum concentration (late 50% t_{max}), time to maximum observed drug concentration (t_{max}), and half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

As plasma treprostinil concentrations after administration of LY900014 are expected to be very low, a descriptive statistical analysis may be conducted if sufficient data are available for this analysis. The primary analysis of the treprostinil concentrations will be focused on assessing t_{max} and C_{max}.

Glucodynamics: The GD assessments will be determined from the euglycemic clamp procedure, where the glucose infusion rate (GIR) over time will be used as a measure of insulin effect. The GD analyses will be conducted on those patients who complete at least 1 clamp procedure.

A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and/or period. The fitted data for each patient will be used to calculate the GD parameters. The values of these GD parameters will be summarized by treatment through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated.

The GD statistical model will be the same as the model used for the analysis of the PK parameters. The following variables will be log-transformed prior to analysis: maximum GIR (R_{max}), total amount of glucose infused (Gtot), total amount of glucose infused over 30 minutes ($Gtot_{[0\text{-}30min]}$), and total amount of glucose infused over 1 hour ($Gtot_{[0\text{-}1h]}$).

The same model without log transformation will be used for the analysis of the GD time parameters: time to onset of insulin action (T_{onset}), time to R_{max} (TR_{max}), time to early half-maximal GIR before TR_{max} (early 50% TR_{max}), and time to half-maximal GIR after TR_{max} (late 50% TR_{max}). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value for the difference between least-squares means will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The analyses described above will also be performed on the population of patients who complete and have evaluable GD data for both study periods.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITRZ

	Screening	Treatment Periods 1 and 2			Follow-up /ED	Comments
Procedure	Within 28 days prior to Day 1	Day -1	Day 1	Day 2	≥14 days after last dose	
Informed Consent	X					The ICF will be signed after sufficient explanation by site staff and sufficient time to understand ICF contents. The study ICF must be signed before any study screening procedures are performed, but this does not have to be within 28 days of treatment start (Day 1). No window is defined; however, the patient will have to re-sign the study ICF in case it has been updated/revised.
Patient Admission to CRU		X				
Patient Discharge from CRU				X		After completion of all study procedures, at the discretion of the investigator. Patients may be discharged before Day 2, but all procedures will be competed.
Overnight Fast	X	X	X			At least 8 hours prior to the screening visit, and at least 8 hours prior to each dose until the end of the euglycemic clamp on Day 1. Up to 20 g of carbohydrates will be allowed to prevent hypoglycemia.
Standardized Meal		X	X			Patients will receive short-acting insulin either via an injection or via a bolus dose from the insulin pump before the start of a standardized dinner on Day -1, 6 hours prior to dosing, and along with the meal given after the euglycemic clamp procedure. If the clamp procedure is completed in <10 hours, then the meal should be delayed until the last PK sample has been taken, unless the investigator deems it necessary.
Run-in & Stabilization of Blood Glucose			X			To start approximately 1 to 6 hours prior to study drug dosing.
Randomization		X				The randomization should be performed on Day -1 after CRU admission in Period 1 only.
Study Drug Administration			X			Time = 0 minutes.
Height	X					
Weight	X		Predose		X	

	Screening	Treatment Periods 1 and 2			Follow-up /ED	Comments
Procedure	Within 28 days prior to Day 1	Day -1	Day 1	Day 2	≥14 days after last dose	
Hip & Waist Circumference		X				Triplicate measurement of hip and waist circumference will be required.
Physical Examination	X	X		X	X	Full physical examination at screening. Symptom-driven physical examination at all other time points. Assessments on Day 2 performed prior to discharge from CRU. If the patient is discharged before Day 2, assessments will be completed before discharge.
Alcohol Breath Test	X	X			X	
Medical Assessment	X	X	X	X	X	Medical history at screening. Medical review at other time points, where appropriate. Assessments on Day 1 performed at end of clamp procedure. Assessments on Day 2 performed prior to discharge from CRU. If the patient is discharged before Day 2, assessments will be completed before discharge.
Adverse Events Monitoring	X	X	X	X	X	
Vital Signs (supine)	X	X	Predose, 0.5, 2 hours		X	Collected after the patient is supine for at least 5 minutes. Body temperature at screening only. Predose vital signs may be collected up to 2 hours before the start of the euglycemic clamp.
12-lead ECGs	X		Predose (triplicate×3), 30, 120 minutes		X	Patients must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. A single local safety ECG will be measured at screening and follow-up. ECGs on Day 1 will be taken in triplicate. Predose triplicate ECGs will be collected 3 times (total 9 ECGs) over a 10-minute interval during the blood glucose stabilization period approximately 30 minutes before dosing and start of the euglycemic clamp.
Clinical Laboratory Tests	X		Up to 2 hours predose in Period 1 only		X	See Appendix 2, Clinical Laboratory Tests, for details. Samples collected after a fast of at least 8 hours. Additional tests may be performed at the discretion of the investigator.
Pregnancy Test	X	X			X	Female patients only. Serum pregnancy test at screening, and urine pregnancy test at all other time points.

	Screening	Treatment Periods 1 and 2			Follow-up /ED	Comments
Procedure	Within 28 days prior to Day 1	Day -1	Day 1	Day 2	≥14 days after last dose	
FSH	X					Women of non-childbearing potential only.
Urine Drug Screen	X					
Injection-site Local Tolerability Assessments			0, 60, 240 minutes postdose, end of clamp procedure			Assessments at time 0 are immediately following dosing.
VAS Assessment of Injection-site Pain			0, 60, 240 minutes postdose, end of clamp procedure			Assessments at time 0 are immediately following dosing.
PK Sampling for Insulin Lispro			Predose (0), 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300, 360, 420, 480, 540, 600 minutes postdose			Sampling times are relative to study drug administration time (0 minutes).
PK Sampling for Treprostinil			15, 30, 60, 120 minutes postdose			Sampling times are relative to study drug administration time (0 minutes).
Euglycemic Clamp			From 0 up to 10 hours postdose			
Blood Glucose Monitoring (Euglycemic Clamp)			X			Every minute during the run-in and for the duration of the euglycemic clamp until up to 10 hours postdose.
Pharmacogenetics Sampling			X			Samples collected predose in Period 1 only.
Immunogenicity Sampling			X		X	Day 1 samples will be collected predose (up to 2 hours prior to dosing) for Period 1 and Period 2. Additional samples may be collected if the investigator considers an AE is possibly immunologically indicated.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; ICF = informed consent form; PK = pharmacokinetic; VAS = visual analog scale.

Note: The site should schedule activities as appropriate. If multiple procedures take place at the same time point, the following order of priorities for the procedures should be used: PK sampling (including blood sampling for blood glucose, immunogenicity, and clinical laboratory tests), ECGs, vital signs, and injection-site local tolerability. Electrocardiograms and vital sign measurements should be scheduled prior, but as close as possible, to PK sampling time points. Injection-site assessments and VAS assessments of injection-site pain can be conducted after PK sampling. If the investigator decides based on clinical judgment not to dose a patient on a given day (eg, because of low blood glucose), the patient's visit may be rescheduled; any procedures performed in that period may be repeated.

3. Introduction

3.1. Study Rationale

LY900014 is an ultra-rapid-acting insulin lispro formulation with an increased early absorption of insulin lispro compared to commercially available insulin lispro (Humalog®, Eli Lilly and Company; Humalog package insert, 2015). LY900014 aims to closely mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions.

The previous study with LY900014 in Japanese healthy subjects used an extemporaneous preparation. The aim of this study is to compare the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) profiles of the proposed LY900014 commercial formulation administered from prefilled pens with those of insulin lispro (Humalog) during a euglycemic clamp in Japanese patients with type 1 diabetes mellitus (T1DM).

3.2. Background

When healthy subjects were administered 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. Although some prandial insulin analogs are absorbed faster than human insulin, the general consensus is that rapid-acting insulin administered SC either by a pump or syringes/pen-injectors is still not rapid enough to match the carbohydrate-absorption profiles, thus limiting efficacy and dosing flexibility. An ultra-rapid-acting prandial insulin would shift the pharmacokinetics (PK)/glucodynamics (GD) of insulin analogs such that they would have an even faster onset to better match carbohydrate absorption.

LY900014 is a novel formulation of insulin lispro that contains treprostinil, sodium citrate, and other excipients. This formulation involves the novel use of a microdose of treprostinil as an excipient to enhance the absorption of insulin lispro by local vasodilation rather than as an active pharmaceutical ingredient to elicit a systemic effect. Treprostinil is a prostacyclin analog, administered either by inhalation [redacted]) or by continuous intravenous (IV) infusion or continuous SC administration ([redacted], for the treatment of symptomatic pulmonary arterial hypertension (PAH). Sodium citrate, an excipient that speeds up insulin absorption, is also included in the formulation to further enhance the absorption of insulin lispro. Sodium citrate and other excipients (zinc chloride and magnesium chloride) in the LY900014 formulation are listed in the US Food and Drug Administration (FDA) Generally Recognized as Safe Food Additives database (FDA 2015a), the US FDA Inactive Ingredients in Approved Drugs database (FDA 2015b), and the concentrations in LY900014 are within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

Safety and tolerability of LY900014 have been demonstrated in 118 healthy subjects, including 15 Japanese, in 3 previous clinical studies across a dose range of 7.5 to 30 U. The 3 studies were Phase 1, randomized, and subject-blind, and the PK and GD of insulin lispro from LY900014 and Humalog were evaluated during a euglycemic clamp following SC administration. The total

insulin lispro exposure and total amount of glucose infused (Gtot) were similar for LY900014 and Humalog; however, LY900014 demonstrated a faster and earlier insulin lispro absorption compared to Humalog.

Additionally, data from 2 Phase 1b studies showed that LY900014 was well tolerated in patients with type 1 diabetes mellitus (T1DM; 60 patients) and in patients with type 2 diabetes mellitus (T2DM; 29 patients) receiving single doses, multiple daily injections (MDI), or continuous subcutaneous insulin infusion (CSII). A further study in 24 patients with T1DM is ongoing. There were no serious adverse events (SAEs) related to study treatment or discontinuations from the studies because of a drug-related adverse event (AE). Across both studies, the numbers of treatment-emergent AEs were low for both LY900014 and Humalog.

More information can be found in the Investigator's Brochure (IB) of LY900014.

3.3. Benefit/Risk Assessment

There is no anticipated therapeutic benefit for the patients participating in this study.

Data from studies with healthy subjects and patients with T1DM or T2DM have shown that LY900014 is well tolerated with an adverse drug reaction profile consistent with that of Humalog.

Potential risks associated with LY900014 are derived from the known risks of insulin lispro (Humalog®; Humalog package insert). These potential risks include hypoglycemia, hypersensitivity reactions (localized allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral oedema (Humalog package insert, Japan, 2016; Humalog interview form, 2017).

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 for CCI [redacted] Based on previous studies of LY900014 with a 15-U dose, the exposures of treprostinil in this study are expected to be undetectable compared to those observed in the dose ranges previously explored with SC bolus administration of treprostinil, and are expected to be substantially lower than those observed in 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.

Following administration of the study insulin (Humalog or LY900014), patients will receive an IV glucose infusion at a variable rate to maintain euglycemia up to 10 hours after insulin administration. The aim of the euglycemic clamp procedure is to maintain blood glucose within the normal glycemic range. The euglycemic clamp is performed while the participant is inpatient and under the investigator's supervision. These considerations should minimize the risk of hypoglycemia in patients participating in CCI [redacted]

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

4. Objectives and Endpoints

Table ITRZ.1 shows the objectives and endpoints of the study.

Table ITRZ.1. Objectives and Endpoints

Objectives	Endpoints
Primary To compare the PK of insulin lispro following administration of a single 15-U SC dose of LY900014 to insulin lispro (Humalog) in Japanese patients with T1DM.	Early 50% t_{max} and $AUC_{(0\text{-}30min)}$
Secondary • To compare the GD during a euglycemic clamp following administration of a single 15-U SC dose of LY900014 or insulin lispro (Humalog) in Japanese patients with T1DM. • To evaluate the safety and tolerability of the proposed commercial formulation of LY900014.	• Early 50% TR_{max}, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1h)}$, and T_{onset} • AEs

Abbreviations: AE = adverse event; $AUC_{(0\text{-}30min)}$ = area under the concentration versus time curve from time zero to 30 minutes; early 50% t_{max} = time to early half-maximal serum concentration; early 50% TR_{max} = time to early half-maximal glucose infusion rate before time to maximum glucose infusion rate; GD = glucodynamic; $Gtot_{(0\text{-}1h)}$ = total amount of glucose infused over 1 hour; $Gtot_{(0\text{-}30min)}$ = total amount of glucose infused over 30 minutes; PK = pharmacokinetics; SC = subcutaneous; T1DM = type 1 diabetes mellitus; T_{onset} = time to onset of insulin action.

5. Study Design

5.1. Overall Design

This is a Phase 1, single center, randomized, patient- and investigator-blind, 2-treatment, 2-period, crossover study to evaluate the PK and GD of insulin lispro following a single 15-U SC administration of LY900014 compared to insulin lispro (Humalog) in Japanese patients with T1DM.

Patients will be randomized to 1 of 2 treatment sequences according to the actual randomization table provided to the site (Section 7.2; Table ITRZ.3). Each patient will participate in a screening visit (may occur up to 28 days prior to dosing), 2 inpatient dosing visits, and a follow-up visit (at least 14 days from last dose). Before each dose, a run-in period of approximately 1 to 6 hours to stabilize blood glucose will occur. Dosing visits will be separated by a washout period of 3 to 28 days, during which patients will resume their normal insulin treatment with the exemption of the insulin switch 48 to 72 hours prior to dosing as mentioned below. At each treatment period, patients will receive either LY900014 or insulin lispro (Humalog) and undergo a euglycemic clamp procedure where the time-concentration and time-action profiles of the study treatment will be evaluated simultaneously for up to 10 hours using an automated clamp device. Briefly, the aim of the euglycemic clamp is to maintain euglycemia after the administration of a dose of insulin by means of variable glucose infusion. The variable glucose infusion maintains or "clamps" glucose at a constant euglycemic target; therefore, the glucose infusion rate (GIR) reflects the GD effect of the insulin.

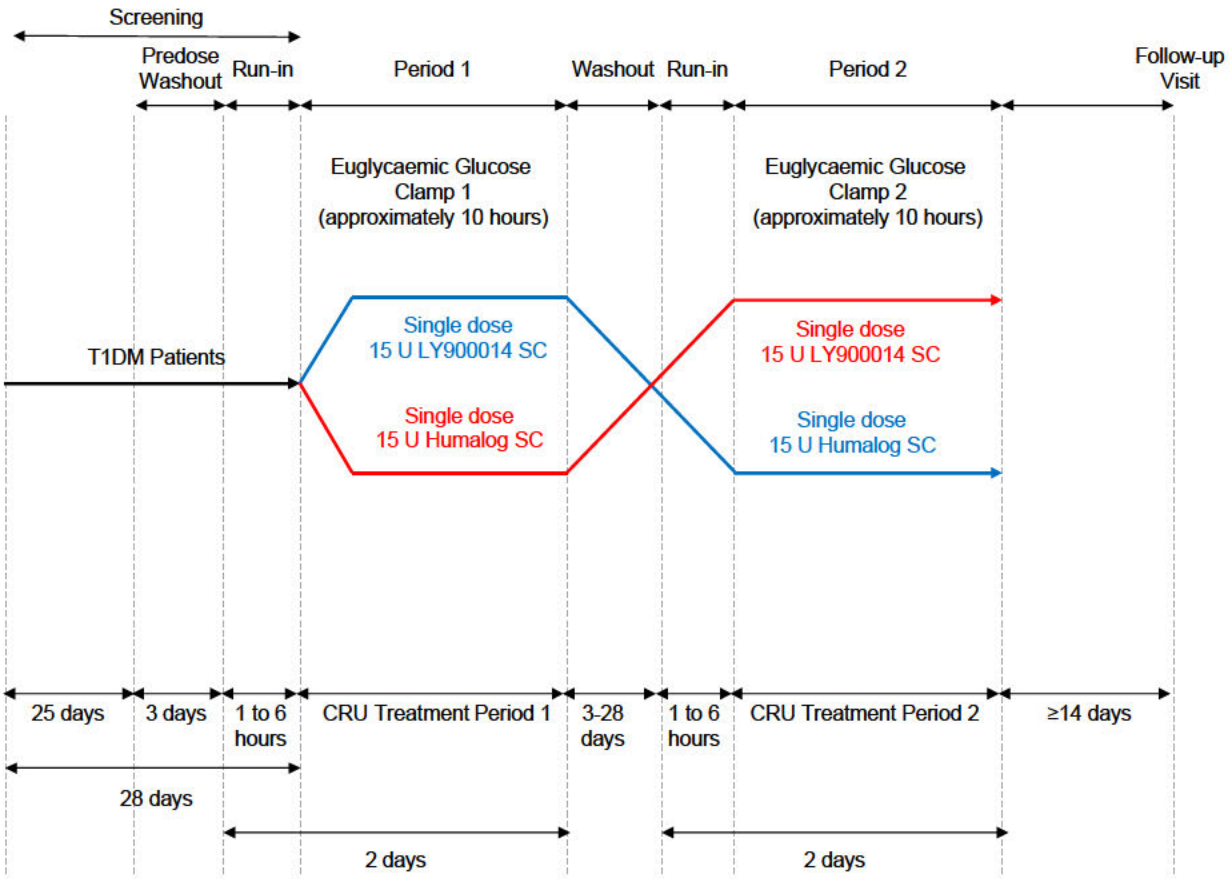
Figure ITRZ.1 illustrates the study design.

Prior to each dosing visit, patients with T1DM on MDI have to discontinue their basal insulin, according to the following guidance:

- For patients using insulin degludec or insulin glargine U300, the last injection of insulin degludec or insulin glargine U300 should occur no later than 72 hours prior to dosing.
- For patients using insulin detemir or glargine, the last injection of insulin detemir or glargine should occur no later than 48 hours prior to dosing.
- For patients using neutral protamine Hagedorn (NPH) insulin or other intermediate-acting insulin, the last injection of NPH insulin or other intermediate-acting insulin should occur no later than 24 hours prior to dosing.

Patients requiring any infusion via CSII of insulin lispro (Humalog) will switch to insulin glulisine ([redacted]) at least 8 hours prior to dosing. Basal infusion rate via CSII should occur no later than 3 hours prior to dosing. Any injection or bolus infusion via CSII of more than 6 U of short-acting insulin should not occur between 11 and 6 hours prior to dosing. Any bolus injection or bolus infusion via CSII should occur no later than 6 hours prior to dosing.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: CRU = clinical research unit; SC = subcutaneous; T1DM = type I diabetes mellitus.

Note: Prior to each dosing visit, patients will discontinue their basal insulin during a washout period of up to 3 days. In both periods, patients may be discharged from CRU after 1 day at the discretion of the investigator and after all assessments are completed.

Figure ITRZ.1. Study design.

5.1.1. Inpatient Dosing Visits

The patient will check into the CRU on Day -1 of each period before his/her evening meal. Patients on MDI are to have discontinued their basal insulin or intermediate-acting insulin as described above; however, patients on CSII should arrive at the CRU with their basal rate running. All patients will receive short-acting insulin either via an injection or via a bolus dose from the insulin pump before the start of a standardized dinner at the CRU. This prandial dose should be administered no later than 6 hours prior to the planned study drug dosing the next day. After dinner, the patient is required to fast until the completion of the clamp procedure the following day. Consumption of food or beverages other than water or barley tea later than approximately 22:00 on the evening before dosing is not allowed, with the exception of minor intake of rapidly absorbable carbohydrates (not more than 20 g) if necessary to prevent hypoglycemia (if carbohydrates have been ingested, patients' blood glucose measurement will have to confirm that they are not hypoglycemic). If hypoglycemia (blood glucose level ≤63 mg/dL [≤ 3.5 mmol/L] or plasma glucose [PG] ≤70 mg/dL [≤3.9 mmol/L]) or more than 20 g of

carbohydrates are needed to prevent hypoglycemia less than 24 hours prior to dosing, the dosing visit can be rescheduled 1 to 7 days later. Each of the dosing visits can only be rescheduled once.

Prior to study treatment dosing, the patient will be connected to the clamp device for continuous glucose monitoring and the start of the baseline run-in period. Variable IV infusion of either glucose (10% to 20% dextrose solution) or insulin glulisine [redacted] will be started to reach a target blood glucose level of 100 mg/dL (Section 9.6.1). Once the target blood glucose level is attained and remains stable, with the predose activities as specified in the Schedule of Activities (Section 2) completed, the patient will receive a dose and undergo the clamp procedure. Serial blood samples will be collected during the 10-hour glucose clamp at times specified in the Study Schedule (Section 2) to assess the GD and the insulin lispro PK following study drug administration. More information on the clamp methodology can be found in Section 9.6.

On completion of the euglycemic clamp, patients will be provided with a meal along with their prandial insulin treatment. A physician's medical assessment will be required before patients are discharged from the CRU.

Safety assessments and an evaluation of local tolerability at injection sites will be performed as specified in the Study Schedule (Section 2).

There are no outpatient visits planned in the washout period.

5.1.2. Outpatient Procedure

After completing each period, patients will resume their previous insulin regimen. The investigator will provide instructions for transition back to a normal insulin regimen.

Patients will return for the second dosing period within a 3- to 28-day interval, during which they will have to perform at least 4-point daily self-monitoring plasma glucose (SMPG). The basal insulin will have to be discontinued as described above in Section 5.1.

After completing all study treatment dosing and clamp procedures, patients will resume their former insulin regimen and SMPG routine. A CRU visit for follow-up or early discontinuation should occur at least 14 days after the last dose of study drug.

5.2. Number of Participants

Up to 40 patients may be enrolled in order that approximately 28 patients complete the study. If patients drop out of the study before completion of both treatment periods with evaluable primary outcome data, replacement patients may be enrolled; the replacement patients will assume the same treatment sequence as the patients who dropped out and will complete that treatment sequence in its entirety.

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 use of a crossover design allows each patient to serve as his or her own control, thereby reducing variability. The study is patient- and investigator-blind to minimize potential bias.

A euglycemic clamp technique, the gold-standard methodology for assessing insulin action, will be used in this study to provide data on the GD activity of each study insulin lispro formulation (see Section 9.6.1 for a detailed description of the clamp methodology).

A population of Japanese patients with T1DM will provide PK and GD profiles for potential comparison to CCI [redacted] results for non-Japanese, young adult patients with T1DM.

Based on the PK properties of treprostinil (half-life associated with the terminal rate constant in noncompartmental analysis [$t_{1/2}$] = approximately 1 hour) and Humalog ($t_{1/2}$ = approximately 0.92 hours), the duration of the washout period between clamp visits (a minimum of 3 days) and the duration between the last dose of study drug and the follow-up visit (at least 14 days) are considered appropriate.

5.5. Justification for Dose

Based on previous studies of both insulin lispro (Humalog) and LY900014, the 15-U dose is within the clinical dose range and should provide measurable PK and GD profiles for both study insulins. The safety, PK, and pharmacology of LY900014 at similar doses and with similar formulation composition have been assessed in 3 clinical studies in healthy subjects CCI [redacted] in patients with T1DM (CCI [redacted] and in patients with T2DM CCI [redacted] In patients with T1DM, the weight-based total daily insulin dose for a large majority of patients is 0.4 to 0.8 U/kg/day, of which approximately 50% is delivered as the basal insulin dose and the other 50% is divided among preprandial insulin doses (Herbst and Hirsch 2002; Heller et al. 2009). Therefore, a reasonably high estimate for total daily preprandial insulin dose in patients with T1DM is 0.4 U/kg/day. For the ongoing CCI [redacted] in non-Japanese patients with T1DM, it was estimated that the lowest body weight would be around 56 kg. Thus, the 15-U dose of LY900014 was selected in CCI [redacted] to deliver approximately a 0.26-U/kg dose, which would not exceed this high estimate for the total daily preprandial insulin dose.

The same 15-U dose of LY900014 is selected in this study to allow for the potential comparison of PK and GD with that of Study ITRR. The expected lowest body weight for this study will be 40 kg (0.375 U/kg) and would not exceed the high estimate for total daily preprandial insulin dose in T1DM.

A 15-U dose of LY900014 contains CCI [redacted] of treprostinil in a single SC dose, which is within the range evaluated as safe and tolerated in all previous studies. The PK of treprostinil in LY900014 following SC administration of 15 U of LY900014 was assessed previously in CCI [redacted] In these studies, treprostinil exposure was not detectable for the 15-U dose of LY900014 (CCI [redacted]). Based on these results, treprostinil blood concentrations in this study are expected to be CCI [redacted]

6. Study Population

Eligibility of patients for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG).

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 28 days prior to enrollment. Patients who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

[1] are Japanese male or female patients with a diagnosis of T1DM, based on the World Health Organization classification, for at least 1 year prior to screening

[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 the 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 not of childbearing potential may participate in the study without using adequate contraceptive methods if they are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian 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, aged ≥52 years and being amenorrheic for less than 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 at least 18 years at the time of screening

[3] have a body mass index (BMI) of 18.5 to 30.0 kg/m2

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

[5] have venous access sufficient to allow for glucose infusion and blood sampling as per the protocol

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

[7] have a glycated hemoglobin <9.0% at screening

[8] have had no episodes of severe hypoglycemia in the last 6 months

[9] are able and willing to give signed 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:

[10] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling

[11] are Lilly employees or employees of the investigative site

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

[13] 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

[14] have previously completed or withdrawn from this study or any other study investigating LY900014, and have previously received the investigational product

[15] have known allergies to insulin lispro, treprostinil, insulin glulisine, related compounds or any components of the formulation, or history of significant atopy

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

[17] have supine systolic blood pressure at screening higher than 160 mmHg or have a heart rate higher than 90 beats/minute. Patients with minor deviations from these ranges may be included as judged by the investigator

[18] have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine (other than 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

[19] have known or ongoing psychiatric disorders

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

[21] show evidence of an acute infection with fever or infectious disease at the time of study entry

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

[23] show evidence of hepatitis C and/or positive hepatitis C antibody (the presence of hepatitis C antibodies in the setting of normal liver function tests and a negative hepatitis C polymerase chain reaction are not an exclusion)

[24] show evidence of hepatitis B and/or positive hepatitis B surface antigen (the presence of antibodies to the hepatitis B surface antigen is not an exclusion)

[25] show evidence of syphilis and/or are positive for syphilis test

[26] are women who are pregnant or lactating

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

[28] have, except for current regimen of insulin therapy and concomitant medication(s) (for example, antihypertensive medication, lipid-lowering agent, thyroid hormone replacement medication, hormonal contraception, hormonal replacement therapy), 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

[29] are unwilling to refrain from smoking while resident at the CRU

[30] 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

[31] have donated 400 mL or more blood in the last 12 weeks (males) or in the last 16 weeks (females), any blood donation (including apheresis) within the last 4 weeks, or total volume of blood donation within 12 months of 1200 mL (males)/800 mL (females) or more at screening

[32] 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 men, or more than 12 g of alcohol per day for women

[33] are unwilling to comply with the dietary and fasting requirements/restrictions during the study, or are unwilling to consume only the meals/snacks provided while resident at the CRU

[34] have a history of renal impairment (exclusion only if estimated glomerular filtration rate [GFR] <60 mL/minute/1.73 m^2 [GFR is estimated according to a formula recommended by the Japanese Society of Nephrology]), or have a serum creatinine level ≥126 μmol/L (>1.42 mg/dL) (male) or ≥111 μmol/L (>1.25 mg/dL) (female)

[35] have a history of deep vein thrombosis of the leg, or repeated episodes of deep leg vein thrombosis in first-degree relatives (parents, siblings, or children), as determined by the investigator

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

[37] have had any significant changes in insulin regimen and/or unstable blood glucose control within the past 3 months prior to screening, as determined by the investigator

[38] require daily insulin treatment >1.5 U/kg

[39] have had lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years

[40] have had breast cancer within the past 10 years

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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [10] and [11] prevent conflict of interest in study participants. Criteria [12] through [41] exclude medical conditions, medication intolerance, and concomitant medication use that may constitute a risk for the patient and/or may confound the assessment of study endpoints.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Patients will receive a standardized dinner on Day -1, and will be fasted (except for water and barley tea) for at least 8 hours prior to collection of clinical laboratory samples, for at least

8 hours prior to dosing, and during the euglycemic clamp procedure, according to the Schedule of Activities (Section 2). Up to 20 g of carbohydrates will be allowed to prevent hypoglycemia, prior to the start of the euglycemic clamp. Water or barley tea can be consumed freely during this time. Patients will be given a meal after the euglycemic clamp procedure is completed. If the clamp procedure is completed in less than 10 hours, then the meal should be delayed until the last PK sample has been taken, unless the investigator deems it necessary to administer the meal for safety reasons.

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 will be encouraged to follow their normal diets.

6.3.2. Caffeine, Alcohol, and Tobacco

Patients should refrain from consuming caffeine-containing food/beverages (eg, cola, chocolate drinks, tea, and coffee) for at least 12 hours prior to each dose and while resident at the CRU.

No alcohol will be allowed from at least 24 hours before and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 24 g for males and 12 g for females.

Smoking (cigars, cigarettes, electronic cigarettes, or pipes) and the use of smokeless tobacco will not be permitted while patients are resident at the CRU.

6.3.3. Activity

Patients will be encouraged to maintain their regular exercise; however, they should not undertake vigorous or prolonged exercise at least 48 hours prior to each dosing day. Should this occur, these patients will have their dosing visits deferred or may be excluded from this study, as judged by the investigator, to prevent interference with study results.

After dosing, patients should remain in the CRU either recumbent or sitting until the end of the glucose clamp. Movement will be restricted to retain the integrity of connections to the glucose clamp and the study procedures.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. The interval between rescreenings should be at least 2 weeks. If rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY900014 administered once by SC injection with Humalog administered once by SC injection. Table ITRZ.2 shows the treatment regimens.

Table ITRZ.2. Treatments Administered

Treatment Name	LY900014	Humalog
Dosage Formulation	100 U/mL	100 U/mL
Dose Level	15 U	15 U
Treprostinil Concentration and Approximate Treprostinil Dose Administered	CCI [redacted]	NA
Route of Administration	Subcutaneous injection	Subcutaneous injection

The investigator or designee is responsible for:

- explaining the correct use of the investigational products to 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 investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

The investigational product will be labeled according to the country's regulatory requirements.

Study insulins (LY900014 and insulin lispro [Humalog]) will be supplied by Lilly or its representative, in accordance with current good manufacturing practices, and will be supplied with clinical trial lot numbers. Instruction for Use for the prefilled devices will be provided.

The prefilled pens will contain a concentration of 100 U/mL in 3-mL cartridges of either LY900014 or insulin lispro (Humalog).

An unblinded pharmacist at the site or other site personnel who are unblinded will prepare to blind the prefilled pen before the treatment administration.

7.1.2. Medical Devices

The medical devices provided for use in the study are prefilled pens. LY900014 prefilled pens are new investigational combination products.

7.2. Method of Treatment Assignment

Patients will be randomized to 1 of 2 treatment sequences indicated in Table ITRZ.3.

Table ITRZ.3. Treatment Sequences

Treatment Sequence	Treatment Period 1	Treatment Period 2
1	15 U LY900014	15 U Humalog
2	15 U Humalog	15 U LY900014

7.2.1. Selection and Timing of Doses

The actual date and time of all dose preparations will be documented, and the actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF). For each patient, the doses will be administered at approximately the same time on Day 1 of each treatment period.

All study treatments will be given in the CRU by qualified CRU personnel as designated by the investigator. Injections should be given by a limited number of individuals for consistency.

Injection sites selected should be about 5 cm from the umbilicus and should be recorded in the patient's eCRF. Injections will be rotated among different injection sites on the anterior abdominal wall during both treatment periods (ie, left lower quadrant and right lower quadrant).

7.3. Blinding

This is a patient- and investigator-blind study. The Lilly clinical pharmacologist (CP)/Lilly study team is unblinded. Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

LY900014 and Humalog will be provided to the CRU in an unblinded manner. An unblinded pharmacist (or designee) will prepare blinded prefilled pens for study drug administration from the LY900014 and Humalog. The patients, investigators, and CRU staff other than the unblinded pharmacist (or designee) will be blinded to the treatment administered.

Emergency codes will be available to the investigator. A code, which reveals the treatment group for a specific study patient, may be opened during the study only if the patient's wellbeing 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. The patient's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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

7.4. Dose Modification

Dose modifications are not allowed in this study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all investigational product received and any discrepancies are reported and resolved before use of the study treatment.

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

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 receiving multiple daily insulin injections will discontinue their basal and prandial insulin regimens as described in Section 5.1 prior to receiving study treatment. Similarly, the patient's insulin regimen should resume in between dosing periods and should be discontinued prior to the next period following the guidance in Section 5.1.

Patients should not use over-the-counter or prescription medications (other than their current regimen of insulin therapy and concomitant medication[s] [for example, antihypertensive medication, lipid-lowering agent, thyroid hormone replacement medication, hormonal contraception, hormonal replacement therapy]) 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, occasional acetaminophen [paracetamol], ibuprofen, or hormonal replacement therapy) or throughout the study (refer to Section 6.2).

Patients should not be 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.

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

If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator and, when possible, after consultation with a Lilly CP. Any additional medication used during the course of the study must be documented.

Any changes in concomitant medications from screening will be recorded upon admission to the CRU.

7.8. Treatment after the End of the Study

Insulin lispro (Humalog) and LY900014 will not be made available from the sponsor to patients after conclusion of the study. Patients will resume their previous insulin regimen after the study procedure has been completed or after discontinuation/early termination from the study.

8. Discontinuation Criteria

Patients discontinuing from the study prematurely for any reason must complete early discontinuation procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

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 CP/ clinical research physician (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 CP/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 study 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.
- the investigator decides that the patient should be discontinued from the study.
- the patient requests to be withdrawn from the study.
- participation in the study needs to be stopped for safety reasons in the case of a severe hypoglycemic episode.

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.

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

Appendix 5 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.

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.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational 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 eCRF, 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, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the investigational product, study device, 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.

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
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above
- when a condition related to the investigational device necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, 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 eCRF after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to 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 patients once they have discontinued from and/or completed the study (the patient summary eCRF 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 reports as related to investigational product or procedure. 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, 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 or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY900014 or Humalog is considered any dose higher than the dose assigned through randomization.

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia can usually be treated with oral glucose. 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. Hypokalemia must be corrected appropriately.

Refer to the IB for LY900014 and/or Product Label for Humalog.

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).

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

9.4.2. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2). At each time point, vital signs should be collected prior to any blood samples. Blood pressure and pulse rate should be measured after at least 5 minutes supine.

Additional vital signs may be measured during each study period if warranted.

9.4.3. Electrocardiograms

For each patient, 12-lead digital ECGs should be collected according to the Schedule of Activities (Section 2). Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational product should be reported to Lilly or its designee as an AE via eCRF.

For each patient, a single 12-lead digital ECG will be collected locally at screening and follow-up or early termination visit according to the Schedule of Activities (Section 2).

Electrocardiograms on Day 1 will be taken in triplicate consecutively at approximately 1-minute interval at predose (baseline), 30, and 120 minutes postdose. The predose triplicate ECGs will be collected 3 times over a 10-minute interval (total 9 ECGs) during the blood glucose stabilization period approximately 30 minutes before administration of LY900014 or Humalog and start of the euglycemic clamp.

Electrocardiograms must be recorded before collecting any blood samples. Patients must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed to ensure high-quality records. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria 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/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.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted before completion of the final study report (in which case, the overread data would be used).

9.4.4. Physical Examination and Medical Assessment

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

9.4.5. Injection-site Local Tolerability Assessments

Injection-site assessments will be performed according to the Schedule of Activities (Section 2) and as clinically indicated. Additional assessments will be performed until resolution, as judged necessary by the investigator.

Local tolerability at the injection site will be evaluated by means of assessments within the following categories: pain (including burning), itching, erythema, edema, and induration/infiltration.

Digital pictures may be taken of the injection site at the time of identification of local intolerability and thereafter, as judged necessary by the investigator. The pictures should include patient number, visit number, time after injection, and a ruler for scaling.

An injection-site reaction should be recorded as either an AE or an SAE according to respective definitions/criteria.

9.4.6. Pain Measurements Using the Visual Analog Scale

Pain measurements will be assessed using the 100-mm validated visual analog scale (VAS) for pain. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection-site pain.

The VAS (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 will be asked to mark the 100-mm line to indicate pain intensity associated with each injection on a scale of 0 (no pain) to 100 mm (worst imaginable pain) according to the Schedule of Activities (Section 2) and as clinically indicated.

As injection-site pain is an expected AE, injection-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 wellbeing of the patient. Analgesia can be prescribed in response to pain and must be documented in the concomitant medication section of the eCRF.

9.4.7. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes

- AEs

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

9.4.7.1. Hepatic Safety

If a study patient experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

- elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.4.7.2. Glucose Monitoring

Hypoglycemia will be described using the following definitions:

Documented Glucose Alert Level (Level 1)

Plasma glucose ≤70 mg/dL (3.9 mmol/L)

- *Documented symptomatic hypoglycemia:* with typical symptoms of hypoglycemia.
- *Documented asymptomatic hypoglycemia:* without typical symptoms of hypoglycemia.
- *Documented unspecified hypoglycemia:* with no information about symptoms of hypoglycemia available. (This has also been called unclassifiable hypoglycemia.)

Documented Clinically Significant Hypoglycemia (Level 2)

Similar criterion as for Level 1, except for threshold PG <54 mg/dL (3.0 mmol/L)

- *Level 2 documented symptomatic hypoglycemia*
- *Level 2 documented asymptomatic hypoglycemia*
- *Level 2 documented unspecified hypoglycemia*

Severe Hypoglycemia (Level 3)

Patient had altered mental status and could not assist in their own care, was semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L]).

Other Hypoglycemia

- *Nocturnal hypoglycemia:* Any documented hypoglycemic event (including severe hypoglycemia) that occurs at night and presumably during sleep. This is captured as hypoglycemia that occurs between bedtime and waking. This definition is more useful than the commonly used approximately 00:00 to 06:00 definition which does not take patients' individual sleep times into consideration, and is consistent with the American Diabetes Association recommendations of reporting events that occur during sleep (ADA 2005). It is also important to collect the actual time when a hypoglycemic event occurred to allow further characterization of hypoglycemia timing (eg, to allow analysis of frequency of events occurring across a 24-hour clock). Nocturnal hypoglycemia may occur at severity Levels 1, 2, or 3.
- *Relative hypoglycemia (also referred to as pseudohypoglycemia [Seaquist et al. 2013])*: An event during which typical symptoms of hypoglycemia occur, that does not require the assistance of another person and is accompanied by PG >70 mg/dL (3.9 mmol/L). The PG value of patients with chronically poor glycemic control can decrease so rapidly that patients may report symptoms of hypoglycemia before their PG concentration falls below 70 mg/dL (3.9 mmol/L). Events with PG ≤70 mg/dL should not be categorized as relative hypoglycemia. Evaluation and statistical analysis of this category is optional. However, if a patient reports a relative hypoglycemia event where assistance from another person was received or the patient experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycemia event, and report it appropriately.
- *Probable symptomatic hypoglycemia:* Symptoms of hypoglycemia were present, but PG measurement was not reported.
- *Overall (or total) hypoglycemia:* This optional category combines most cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). It does not include relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in the category of overall (or total) hypoglycemia.

Only severe hypoglycemic episodes will be reported separately as AEs. All episodes of severe hypoglycemia will be reported as SAEs.

The goal of the euglycemic clamp is to maintain blood glucose concentrations at euglycemic levels close to a predefined target. Therefore, glucose concentrations below 70 mg/dL will not routinely be recorded as hypoglycemic events during the glucose clamp procedure. However, at the discretion of the investigator, a decrease in glucose concentration may be recorded as a hypoglycemic event based on clinical concern or related to technical issues resulting in hypoglycemia.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2.5 mL each will be collected to determine the serum concentrations of insulin lispro and samples of approximately 2.0 mL each will be collected to determine plasma concentrations of treprostinil. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

9.5.1. Bioanalysis

Serum concentrations of insulin lispro will be measured using a validated CCI [redacted] specific for insulin lispro at a laboratory approved by the sponsor. Plasma concentrations of treprostinil will be measured using a CCI [redacted] at a laboratory approved by the sponsor.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last patient visit for the study. During this time, plasma and serum remaining may be used for other exploratory analyses on insulin lispro or treprostinil.

9.6. Pharmacodynamics

9.6.1. Glucodynamics

The aim of the euglycemic clamp is to maintain euglycemic through infusion of a 10% to 20% glucose solution after the administration of a dose of insulin. During the euglycemic clamp, the GIR will be adjusted to maintain a predetermined target blood glucose concentration for the individual patients. Thus, blood glucose concentrations are kept constant while the GIR varies, and the varying GIR will reflect the GD activity of insulin.

9.6.1.1. Euglycemic Clamp Procedure

Patients will participate in 2 euglycemic clamps across 2 treatment periods. After at least 8 hours overnight fast, the euglycemic clamp procedure will be performed for approximately 10 hours following administration of a dose of insulin lispro according to the Schedule of Assessments (Section 2) and as described in Section 5.1.

Approximately 1 to 6 hours before the planned administration of study drug, patients will be connected to the clamp device CCI [redacted] for continuous blood glucose monitoring and receive a variable IV infusion of either insulin glulisine or glucose to obtain a

steady blood glucose clamp target of 100 mg/dL (±20%) (5.5 [±1.1] mmol/L). The target blood glucose level of 100 mg/dL (5.5 mmol/L) ±20% (upper and lower limits included) must be kept at -60 to -30 minutes before trial product administration, followed by the target blood glucose level of 100 mg/dL (5.5 mmol/L) ±10% (upper and lower limits included) within the last 30 minutes prior to trial product administration without any glucose infusion. The IV insulin glulisine infusion (if any) is lowered as much as possible to keep the blood glucose concentrations at the target without having to infuse glucose. The insulin glulisine infusion is tapered off and should be stopped 10 minutes [redacted] minutes before trial product administration as measured by CCI, and the onset of study insulin action occurs when blood glucose drops to 5 mg/dL (0.3 mmol/L) from baseline. If there are no stable blood glucose measurements with CCI in the last minutes before intended dosing, dosing should be postponed and the run-in period will be prolonged. If the target blood glucose level cannot be established before 14:00, the visit will be terminated and the patient may be rescheduled for a new dosing visit 1 to 7 days later. After the onset of action has been reached, a variable IV glucose infusion will be initiated in order to keep blood glucose constant at the target level. The GIR necessary to keep the blood glucose concentration at the target level will be recorded using a validated data capture system at the CRU.

The clamp procedure will continue for up to 10 hours after dose or until after blood glucose concentrations increased to >200 mg/dL (11.1 mmol/L) without any glucose being administered for at least 30 minutes, whichever is earlier.

At the end of the clamp procedure, the patient will receive a medical assessment and be given a meal along with their prandial insulin treatment. Their basal insulin regimen may be restarted accordingly, albeit subjected to the stopping guidance as described in Section 5.1, prior to the next dosing visit, if applicable.

9.6.2. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro as described 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 by a validated assay designed to detect antidrug antibodies in the presence of insulin lispro.

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 LY900014. Any samples remaining after 15 years will be destroyed.

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 exposure or response to LY900014 and to investigate genetic variants thought to play a role in diabetes mellitus. 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. 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, multiplex assays, 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. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 40 patients will be randomized in order that approximately 28 patients complete the study. Twenty-eight completing patients will provide approximately 92% power to demonstrate a 40% increase in the insulin lispro area under the concentration versus time curve (AUC) from time zero to 30 minutes ($AUC_{[0\text{-}30min]}$) between LY900014 and Humalog. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The variability was estimated by analyzing a Lilly internal study that showed a log-scale standard deviation of within-patient difference in $AUC_{(0\text{-}30min)}$ of 0.5. Analysis of internal data showed a log-scale standard deviation of within-patient difference in time to early half-maximal serum concentration (early 50% t_{max}) of 0.5, which provides approximately 95% power to show a 30% reduction in early 50% t_{max}, testing with an alpha level of 0.05 and a 2-sided CI.

In addition, the study is adequately powered to evaluate the GD parameters. There is approximately 71% power to detect a 20% decrease in both time to onset of insulin action (T_{onset}) and time to early half-maximal GIR before time to maximum glucose infusion rate (TR_{max}) (early 50% TR_{max}), and approximately 81% power to detect at least a 40% increase in total amount of glucose infused over 30 minutes ($Gtot_{[0\text{-}30min]}$) and total amount of glucose infused over 1 hour ($Gtot_{[0\text{-}1h]}$). In estimations, the log-scale standard deviation of within-patient difference was used with 0.45 for T_{onset} and early 50% TR_{max}, and 0.6 for $Gtot_{(0\text{-}30min)}$ and $Gtot_{(0\text{-}1h)}$.

Patients who discontinue from the study prior to completion of both treatment periods with evaluable primary outcome data can be replaced to ensure that enough patients may complete the study. The replacement patient will adopt the original patient's randomized treatment sequence.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of patient disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

The patient's age, sex, weight, BMI, waist and hip circumference, height, race/subrace, and other demographic characteristics will be summarized.

10.3. Statistical Analyses

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

The primary statistical analyses for PK will be conducted on those patients who receive at least 1 dose of study drug and have measurable and evaluable insulin lispro concentrations. The primary statistical analysis for GD will be conducted on those patients who complete at least 1 clamp procedure and have evaluable GD parameters.

Supportive analyses will be done on the key parameters for the patients who complete all treatment periods with evaluable data. Safety analyses will be conducted for all enrolled patients, whether or not they complete all protocol requirements.

Any change in 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.

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented for continuous variables. A linear mixed-effect model will be used for continuous variables unless otherwise stated in the below subsections. The primary comparison between LY900014 and insulin lispro (Humalog) will be performed using the model that includes treatment, sequence, and period as fixed effects, and patient within sequence as a random effect.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure 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 prior to 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, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.1.2.1. Statistical Evaluation of the Intensity of Injection-site Pain

The primary study assessment will be the intensity of pain at each injection site immediately after the injection (time 0) as reported by the patient and measured according to the 0- to 100-mm VAS. A Wilcoxon signed rank test will be used to analyze the time 0 (immediately after dosing) data. A descriptive summary will be provided for the following categories of scores: 0, 1-10, 11-20, 21-30, 31-40, etc. up to the maximum category by treatment for each time point.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Patients who receive at least 1 dose of study drug and have measurable insulin lispro concentrations will be included in the PK analysis dataset.

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

Free serum insulin lispro concentrations will be used to calculate several PK parameters, including: early 50% t_{max}, time to late half-maximal serum concentration (late 50% t_{max}), maximum observed concentration (C_{max}), time to maximum observed drug concentration (t_{max}), $t_{1/2}$, AUC from time zero to the last recorded time, $AUC_{(0\text{-}30min)}$, AUC from time zero to 1 hour, AUC from time zero to 10 hours, and AUC from time zero to infinity. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary. The primary insulin lispro PK parameters for faster insulin lispro absorption analysis are early 50% t_{max} and $AUC_{(0\text{-}30min)}$.

Given the predicted low systemic concentrations of treprostinil, the PK analysis of treprostinil from the LY900014 dosing will be conducted using the available data. The primary analysis of the treprostinil concentrations will be focused on assessing t_{max} and C_{max}.

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

10.3.2.2. Pharmacokinetic Statistical Inference

Log-transformed C_{max} and AUC estimates for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog, and their corresponding 95% CIs using the mixed-effects model that includes treatment, sequence, and period as fixed effects and patient within sequence as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters (early 50% t_{max}, late 50% t_{max}, t_{max}, and $t_{1/2}$). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

Statistical significance will be achieved when the p-value for a test is less than 0.05.

The analyses described above will also be performed on the population of patients who completed and had evaluable PK data for both study periods.

As plasma treprostinil concentrations after administration of LY900014 are expected to be very low, a descriptive statistical analysis may be conducted if sufficient data are available for this analysis.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Glucodynamic Parameter Estimation

Glucodynamic assessments will be determined from the euglycemic clamp procedure, where the GIR over time will be used as a measure of insulin effect. Glucodynamic analyses will be conducted on those patients who complete at least 1 clamp procedure.

A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and/or period using CCI [redacted]. The fitted data for each patient will be used to calculate the following GD parameters: maximum GIR (R_{max}), TR_{max}, early 50% TR_{max}, time to half-maximal GIR after TR_{max} (late 50% TR_{max}), T_{onset}, Gtot over the duration of the clamp procedure, $Gtot_{(0\text{-}1h)}$, and $Gtot_{(0\text{-}30min)}$.

The values of these GD parameters will be summarized by treatment group through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated. The primary GD parameters for analysis are early 50% TR_{max}, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1h)}$, and T_{onset}.

Additional partial glucose AUCs, such as Gtot over 2 hours ($Gtot_{[0\text{-}2h]}$) and Gtot from 3 hours to 10 hours ($Gtot_{[3\text{-}10h]}$), may be computed as necessary.

10.3.3.2. Glucodynamic Statistical Inference

The GD statistical model will be the same as the model used for the analysis of the PK parameters. The following variables will be log-transformed prior to analysis: R_{max}, Gtot, $Gtot_{(0\text{-}30min)}$, and $Gtot_{(0\text{-}1h)}$. Additional partial glucose AUCs, such as $Gtot_{(0\text{-}2h)}$ and $Gtot_{(3\text{-}10h)}$, may be analyzed as necessary. For GD parameters that have at least 1 patient with a value equal to zero, a value equal to the smallest non-zero observed GD value for that parameter divided by 2 will be added to all values, and the analysis of the log-transformed data will be performed. In addition, as a sensitivity analysis, a nonparametric analysis will be performed for that parameter.

The same model without log transformation will be used for the analysis of the GD time parameters (T_{onset}, TR_{max}, early 50% TR_{max}, and late 50% TR_{max}). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value for the difference between least-squares means will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The analyses described above will also be performed on the population of patients who complete and have evaluable GD data for both study periods.

10.3.4. Interim Analyses

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

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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
AUC	area under the concentration versus time curve
$AUC_{(0\text{-}30min)}$	area under the concentration versus time curve from time zero to 30 minutes
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BMI	body mass index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed 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 study-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.
CP	clinical pharmacologist

CRF	case report form
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.
CSII	continuous subcutaneous insulin infusion
early 50% t_{max}	time to early half-maximal serum concentration
early 50% TR_{max}	time to early half-maximal glucose infusion rate before time to maximum glucose infusion rate
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GD	glucodynamic(s)
GFR	glomerular filtration rate
GIR	glucose infusion rate
Gtot	total amount of glucose infused
$Gtot_{(0-30min)}$	total amount of glucose infused over 30 minutes
$Gtot_{(0-1h)}$	total amount of glucose infused over 1 hour
$Gtot_{(0-2h)}$	total amount of glucose infused over 2 hours
$Gtot_{(3-10h)}$	total amount of glucose infused from 3 hours to 10 hours
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization

informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient'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 study 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 study, 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 study at a study site. If a study is conducted by a team of individuals at a study 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 serum concentration
late 50% TR_{max}	time to half-maximal glucose infusion rate after time to maximum glucose infusion rate
LOESS	locally weighted scatterplot smoothing
MDI	multiple daily injections
non-investigational product	A product that is not being tested or used as a reference in the clinical study, 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.
NPH	neutral protamine Hagedorn
randomize	The process of assigning patients to an experimental group on a random basis.
PAH	pulmonary arterial hypertension
PG	plasma glucose
PK	pharmacokinetic(s)
R_{max}	maximum glucose infusion rate
SAE	serious adverse event
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SMPG	self-monitoring plasma glucose

SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time to maximum observed drug concentration
T_{onset}	time to onset of insulin action
TR_{max}	time to maximum glucose infusion rate
ULN	upper limit of normal
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology [a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Absolute counts of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

Urinalysis [a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite

Pregnancy test [a,b]
- hCG

Clinical Chemistry [a]
- Sodium
- Potassium
- Chloride
- Calcium
- Phosphorus
- C-peptide (fasting)
- Glucose (fasting) [c]
- Blood urea nitrogen (BUN)
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine
- Gamma-glutamyl transferase (GGT)

Other [a,d]
- HbA1c
- Hepatitis B surface antigen
- Hepatitis C core antibody
- HIV antigen and antibody
- Syphilis
- Ethanol testing[e]
- Urine drug screen
- FSH[f]

Abbreviations: FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

[a] Performed at local laboratories.

[b] Female patients only. Serum pregnancy test at screening, and urine pregnancy test at other time points.

[c] Plasma glucose measured after a fast of at least 8 hours.

[d] Performed at screening only.

[e] Ethanol testing may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.

[f] Only applicable at screening for menopausal women, if necessary.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator or appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonization (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 and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of patient personal information collected will be provided in a written document to the patient by the sponsor.

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	
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 (direct) bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline phosphatase isoenzymes[a]**
GGT	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
CK	

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

a Assayed by Lilly-designated 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.

Protocol I8B-MC-ITRZ Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening	29	1	29
Clinical laboratory tests[a]	13	2	26
Pharmacokinetics - insulin lispro	2.5	50	125
Pharmacokinetics - treprostinil	2	8	16
Blood glucose monitoring during euglycemic clamp[b]	32	2	64
Insulin level during run-in period	2	2	4
Immunogenicity	5	3	15
Pharmacogenetics	10	1	10
Total			289

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

[b] Blood glucose monitoring: up to 6-hour run-in + 10-hour clamp = 16 hours per period of blood sampling. 16 hours × 2 mL/hour = 32 mL of blood sampling per period.

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