Protocol I8B-MC-ITRU A Study of LY900014 in Participants With Type 2 Diabetes Mellitus
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Protocol I8B-MC-ITRU
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog Following a Single Dose in Patients with T2DM

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Confidential Information

LY900014

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly on date provided below.

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1. Protocol Synopsis

Title of Study:
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog Following a Single Dose in Patients with T2DM

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

The aim of this study is to compare the insulin lispro pharmacokinetic (PK), glucodynamic (GD), safety and tolerability profiles of insulin lispro following administration of either LY900014 or Humalog during a euglycaemic glucose clamp in patients with type 2 diabetes mellitus (T2DM).

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To evaluate the PK of insulin lispro following administration of a single 15 U subcutaneous (SC) dose of LY900014 compared to Humalog in patients with T2DM	Time to early half-maximal drug concentration (early 50% t_{max}) and area under the concentration versus time curve (AUC) from time zero to 30 minutes (AUC[0-30min])
Secondary	
1. To compare the euglycaemic clamp GD of insulin lispro following administration of a single 15 U SC dose of LY900014 or Humalog in patients with T2DM	1. Time to early half-maximal glucose infusion rate (early 50% tR_{max}), total amount of glucose infused (Gtot) over 30 minutes ($Gtot_{[0-30min]}$) and time to onset of insulin action (t_{onset})
2. To evaluate the tolerability of LY900014	2. Adverse events (AEs) and injection site reactions

Summary of Study Design:

Study I8B-MC-ITRU is a randomised, patient- and investigator-blind, 2-treatment, 2-period, 10-hour euglycaemic clamp crossover study in patients with T2DM.

Treatment Arms and Planned Duration:

Patients will be randomised to 1 of 2 treatment sequences according to the actual randomisation table provided to the site. All treatment procedures will be inpatient stays of 2 days per period and require a maximum 5 weeks to complete 2 periods. A minimum period of 72 hours is required between each 10-hour clamp visit during which patients will resume their normal insulin treatment following instructions from the site investigator. The follow-up or early discontinuation visit should occur at least 14 days after the last dose of the study drug.

LY900014: Single 15 U dose

Humalog: Single 15 U dose

Number of Patients:
Up to 42 patients may be enrolled to ensure at least 34 patients complete the study.

Statistical Analysis: Primary statistical analyses will be conducted on the set of patients who complete at least the first period of treatment. Supportive analyses will be done on the key parameters for the patients who complete all treatment periods. Statistical significance will be achieved when the p-value for a test is less than 0.05.

Safety: Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements. Safety assessments including, but not limited to vital signs, safety laboratory parameters, investigational product, procedural and protocol AEs will be captured and summarised using descriptive statistical methodologies.

Pharmacokinetics: PK analyses will be conducted on all patients receiving at least 1 dose of study drug and have evaluable PK. PK analyses will be conducted using standard noncompartmental method of analysis. PK parameters will be assessed using free serum insulin lispro.

Log-transformed PK parameters 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 (early 50% t_{max}, time to late half-maximal drug concentration [late 50% t_{max}], time to maximum observed drug concentration [t_{max}], and half-life associated with the terminal rate constant in non-compartmental 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.

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

Glucodynamics: Glucodynamic assessments (GD) will be determined from the glucose clamp procedure, where the glucose infusion rate (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 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 following GD parameters:

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}), Gtot, Gtot over 30minute (Gtot[0-30min]), and Gtot over 1 hour (Gtot[0-1h]).

The same model without log transformation will be used for the analysis of the GD time parameters (t_{onset}, time to R_{max} (tR_{max}), time to half-maximal GIR before tR_{max} (early 50% tR_{max}), 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 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 completed and had evaluable GD data for both study periods.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITRU

	Screening	Euglycaemic Clamp Procedure Periods 1 and 2		Follow-up/Early Discontinuation	Instructions/Comments
Procedure	Up to -28 days	Day -1	Day 1	At least 14 days after discharge	
Informed consent	X				Informed consent must be signed at least 1 day prior to screening procedures
Admission to CRU		X			Admission to site at early evening
Overnight fast			X		Patients are expected to fast for approximately 8 hours prior to screening and approximately 8 hours before each dose until the end of the glucose clamp procedure
Hip and waist circumference		X			Period 1 only. Measurements taken in triplicate
Height	X				
Weight	X	X			Period 1 only
Medical history and physical examination	X				
Medical assessment		X	Predose and before discharge from CRU for each period	X	Medical assessment includes medical review and targeted examination as appropriate
Vital signs (supine): body temperature, blood pressure and pulse rate	X		Predose and approximately 10 hours postdose (at the end of the clamp procedure)	X	
12-lead ECG	X		Predose and approximately 10 hours postdose (at the end of the clamp procedure)	X	Single ECGs will be collected for safety
Clinical laboratory tests	X		Predose for Period 1 only	X	Fasting laboratory test for screening, Period 1 only as well as for follow-up or early discontinuation. To

					monitor patient safety, additional tests may be performed at the discretion of the investigator as needed throughout the study. Screening laboratory tests are analysed at a local facility
Pregnancy test	X	X		X	For female patients of childbearing potential only. A serum pregnancy test will be performed at screening, analysed at a local laboratory, and urine pregnancy tests will be performed at Day -1 of Period 1 and at follow-up and processed on site
Run-in and stabilisation of glucose			X		To start approximately 1 to 6 hours prior to study drug dosing to achieve blood glucose target of 100 mg/dL (±20%) through the use of infusion of glucose (dextrose solution) or insulin glulisine. See Section 5.1.1 for rescheduling.
Study drug administration			X		Time 0: Study drug administration
Injection-site local tolerability assessments			0, 60, 240 and 600 minutes postdose		Time 0: Assessments of injection-site local tolerability will occur immediately following the injection
VAS Pain assessment			0, 20 and 60 minutes postdose		Time 0: Assessments of injection-site pain will occur immediately following the injection
Insulin lispro PK sampling			0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300, 360, 420, 480, 540 and 600 minutes		Time 0: Sample to be taken immediately before study drug administration. Sampling times are relative to the time of study treatment administration (t = 0).
Blood glucose sampling (euglycaemic clamp)			Blood glucose monitoring every minute starting from the run-in and throughout the duration of the clamp until 10 hours		

			after dosing		
Blood glucose sampling (Super GL)			Approximately every 30 minutes throughout the euglycaemic clamp procedure		
C-peptide sampling			0, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540 and 600 minutes		Time 0: Sample to be taken immediately before study drug administration. Sampling times are relative to the time of study treatment administration (time = 0).
Pharmacogenetics sample			Predose for Period 1 only		Refer to sample collection instructions provided by the sponsor
Immunogenicity sample			Predose for Periods 1 and 2	X	Additional samples may be collected if the investigator considers there is a possibility that an AE is immunologically indicated
Discharge from CRU			X		Patients may be discharged after completion of all study procedures on Day 1. Investigator's discretion to discharge on Day 2

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; PK = pharmacokinetics; VAS = visual analogue scale.

Note: The site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, the order of priority will be as follows: PK samples including blood sampling for blood glucose and laboratory samples per protocol nominal times. ECGs and vital sign measurements should be scheduled before but as close as possible to the PK sampling times. VAS and injection-site assessments can be done after PK sampling.

3. Introduction

3.1. Study Rationale

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

The aim of this study is to compare insulin lispro pharmacokinetic (PK) profiles and glucodynamic (GD) profiles following administration of either LY900014 or Humalog during a euglycaemic glucose clamp in patients with type 2 diabetes mellitus (T2DM).

3.2. Background

The insulin analogue insulin lispro (Humalog®) has been shown to be absorbed more quickly than regular human insulin (Humalog package insert, 2015). In healthy volunteers given subcutaneous (SC) doses of insulin lispro ranging from 0.1 to 0.4 U/kg, peak serum levels were seen 30 to 90 minutes after dosing (Humalog package insert, 2015). However, the general consensus is that rapid-acting insulin is still not rapid enough to match carbohydrate absorption profiles, which limits efficacy and dosing flexibility. An ultra-rapid-acting prandial insulin would shift the PK/GD of insulin analogues so that they have an even faster onset to better match carbohydrate absorption.

LY900014 represents a new formulation that contains insulin lispro, treprostinil, citrate and other excipients. This formulation involves the novel use of a microdose of treprostinil (CCI [redacted]) as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient to elicit a systemic effect. Treprostinil is a prostacyclin analogue, administered either through inhalation (CCI [redacted]), as an intravenous (IV) infusion or as a continuous SC administration for the treatment of symptomatic pulmonary arterial hypertension (PAH) and has been approved in the US since 2002 and in Germany since 2007 (CCI [redacted]). Sodium citrate, an excipient that speeds insulin absorption (likely in part by enhancing vascular permeability), is also included in the formulation to further enhance the absorption of insulin lispro. Each of the other excipients (such as sodium citrate and magnesium chloride) in the LY900014 formulation is listed in the US Food and Drug Administration (FDA)'s Generally Recognized as Safe Food Additives database and in the FDA's Inactive Ingredients in Approved Drugs database. Furthermore, the excipient concentration in LY900014 is within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

Safety and tolerability of LY900014 have been demonstrated in approximately 71 healthy subjects in 3 previous clinical studies, across a dose range of 7.5 to 30 U. All 3 studies were Phase 1, randomised, subject-blind studies in which the PK and GD of insulin lispro from LY900014 and Humalog were evaluated during a euglycaemic glucose clamp following SC administration. The total insulin lispro exposure and GD effect were similar for LY900014 and

Humalog; however, LY900014 demonstrated a faster and earlier insulin lispro absorption compared to Humalog.

In addition, data from two Phase 1b studies showed LY900014 were well tolerated in patients with type 1 diabetes mellitus (T1DM; 30 patients) and in patients with type 2 diabetes mellitus (T2DM; 30 patients) using multiple daily injections (MDIs). There were no serious adverse events (SAEs) related to study treatment or discontinuations from the studies because of a drug-related adverse event (AE). Small numbers of treatment-emergent adverse events were reported, and there were no notable increases in these events in relation to any of the previous LY900014 formulations compared to those in relation to Humalog.

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

3.3. Benefit/Risk Assessment

Study I8B-MC-ITRU (ITRU) will not offer any direct benefits to the patients participating in the study. Data from studies with healthy subjects and patients with T1DM and patients with 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). These potential risks include hypoglycaemia, hypersensitivity reactions (localised allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy) and peripheral oedema (Humalog package insert, 2015).

Notably, across all doses in the 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, CCI [redacted]. The exposures of treprostinil in LY900014 in this trial 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.

In preclinical safety pharmacology and toxicity studies, or clinical pharmacology studies involving LY900014 or treprostinil alone, other than known risks associated with Humalog and Remodulin, no additional risks were identified. 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 Remodulin do not suggest the potential for additive or synergistic toxicity.

In order for patients to participate in this study, they must discontinue use of certain oral antidiabetic (OAD) medications 2 weeks prior to Period 1, Study Day -1 (see Section 5.1). Additionally, patients are required to discontinue their basal insulin prior to Study Day -1 according to the guidance in Section 5.1. Appropriate measures will be taken to minimise the risk of hyperglycaemia (see Section 6.3.4).

Following administration of the study insulin (Humalog or LY900014), patients will receive IV glucose infusion at a variable rate to maintain euglycaemia up to 10 hours after insulin lispro administration. The aim of the clamp procedure is to maintain blood glucose within the normal glycaemic range. In addition, the clamp is performed while the participant is inpatient and under the investigator's supervision. These considerations should minimise the risk of hypoglycaemia in patients participating in Study ITRU.

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

4. Objectives and Endpoints

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

Table ITRU.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
1. To evaluate the PK of insulin lispro following administration of a single 15 U subcutaneous dose of LY900014 compared to Humalog in patients with T2DM	1. Early 50% t_{max} and AUC(0-30min)
Secondary	
1. To compare the euglycaemic clamp GD of insulin lispro following administration of a single 15 U SC dose of LY900014 or Humalog in patients with T2DM	1. Early 50% tR_{max}, $Gtot_{(0-30min)}$ and t_{onset}
2. To evaluate the tolerability of LY900014	2. AEs and injection-site reactions
Exploratory	
1. Explore the formation of anti-drug antibodies to insulin lispro	1. Anti-insulin lispro antibodies
2. To assess C-peptide levels following administration of LY900014 and Humalog	2. C-peptide concentration

Abbreviations: AE = adverse event; AUC(0-30min) = area under the concentration versus time curve from time zero to 30 minutes; early 50% t_{max} = time to early half-maximal drug concentration; early 50% tR_{max} = time to early half-maximal glucose infusion rate; GD = glucodynamics; $Gtot_{(0-30min)}$ = total amount of glucose infused over 30 minutes; PK = pharmacokinetics; SC = subcutaneous; T2DM = type 2 diabetes mellitus; t_{onset} = time to onset of insulin action.

5. Study Design

5.1. Overall Design

ITRU is a Phase 1, randomised, patient- and investigator-blind, 2-treatment, single-dose, 2-period, 10 hour glycemic clamp, crossover study that evaluates the PK and GD of insulin lispro following administration of a single 15 U SC dose of either LY900014 or Humalog in patients with T2DM. Study ITRU may be conducted at 1 or more sites. Figure ITRU.1 illustrates the study design. Patients will be required to attend at the clinical research unit (CRU) on at least 5 occasions as noted in Study Schedule (see Section 2):

- informed consent
- screening
- inpatient study Periods 1 and 2
- follow-up or early discontinuation

Patients will be required to visit the CRU to sign the informed consent form (ICF). Once the ICF is signed, patients will return to the CRU in a fasted state to participate in the screening procedures. Screening procedures may be completed up to 28 days prior to randomisation.

Prior to CRU admission on Day -1 of Period 1, patients with T2DM receiving OAD medication should discontinue their medication according to the following guidance (patients can continue taking metformin throughout the study):

- At most, 2 weeks prior to Day -1 of Period 1, patients should discontinue dipeptidyl peptidase (DPP)-IV inhibitors, sulphonylureas and sodium-glucose co-transporter (SGLT)-2 inhibitors

Prior to each dosing visit, patients with T2DM on multiple daily insulin injections have to discontinue their basal insulin, according to the following guidance:

- For patients using insulin glargine U300, the last injection 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, insulin mixtures 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.
- Any injection of more than 6 U of short-acting insulin should occur between 11 and 6 hours prior to dosing. Any injection should occur no later than 6 hours prior to dosing.

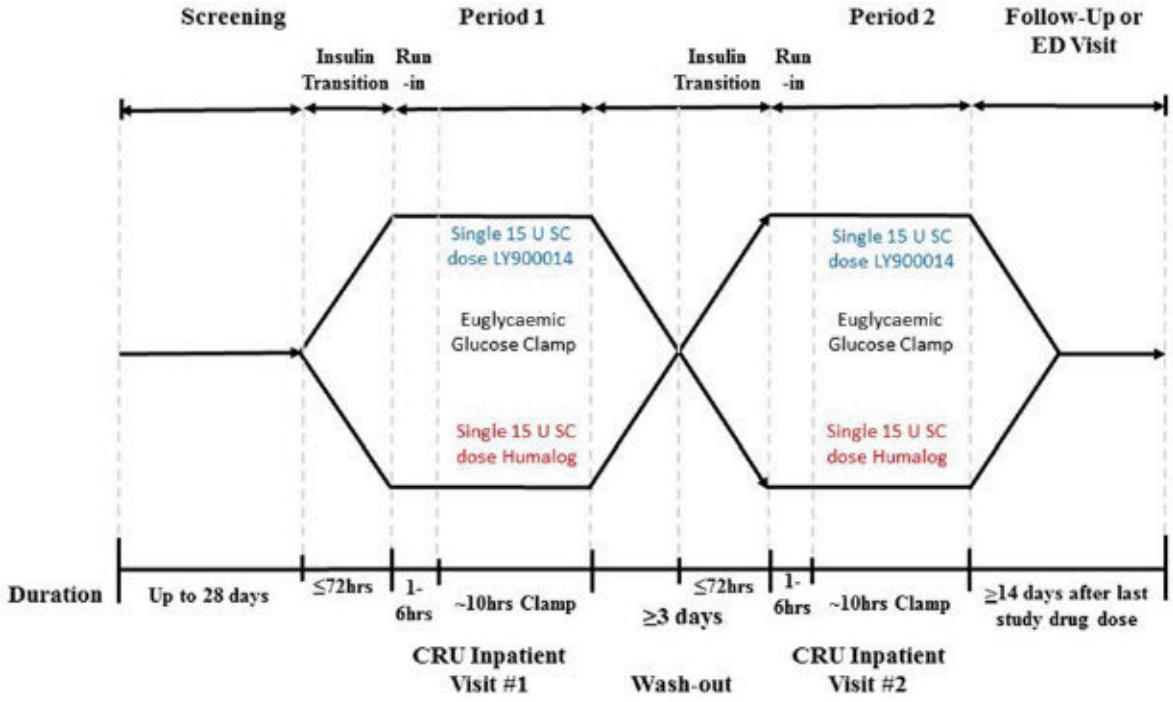
All patients will be instructed to perform at least 4-point daily self-monitoring plasma glucose (SMPG), as well as continue their short-acting insulin during insulin transition period (see Section 6.3.4). A diary will be provided to patients in order for SMPG results and prandial

insulin doses to be recorded during the insulin transition period. The patients' diary will serve as a source document.

After satisfying the study entry criteria, each patient will be randomised to 1 of 2 treatment sequences according to the actual randomisation table provided to the site. Each study period will be separated by a wash-out period of at least 72 hours. Each patient will participate in 2 inpatient visits; at each visit, the time-concentration and time-action profiles will be evaluated simultaneously during a euglycaemic glucose clamp of approximately 10 hours. The maximum duration allowed for both periods is 5 weeks. Briefly, the aim of the euglycaemic clamp is to maintain euglycaemia after the administration of a dose of insulin by means of variable glucose infusion. The variable glucose infusion maintains or "clamps" glucose to a constant euglycaemic target.

Patients will return to the CRU at least 14 days following last dose of study drug for follow-up or early discontinuation procedures.

Figure ITRU.1 illustrates the study design.



Abbreviations: CRU = clinical research unit; ED = early discontinuation; SC = subcutaneous.

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

5.1.1. Inpatient Dosing Visits

The patient will check into the CRU on Day -1 of each period in the early evening. Patients on multiple daily insulin injections would have discontinued their basal insulin. All patients will receive an injection of short-acting insulin (e.g., insulin glulisine) before the start of a standardised dinner within the CRU. 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 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 hypoglycaemia (if carbohydrates have been ingested, patients' blood glucose measurement will have to confirm that they are not hypoglycaemic). If hypoglycaemia (blood glucose level ≤3.5 mmol/L [≤63 mg/dL] or plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) or more than 20 g of carbohydrates are needed to prevent hypoglycaemia 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 (20% dextrose solution) or insulin (insulin glulisine) will be started to reach a target blood glucose level of 100 mg/dL (±20%) during the run-in period. 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 (Section 9.6).

Upon completion of the clamp procedure, the patient may be offered a meal. It is planned that patients will be discharged from the CRU after completion of all study procedures on Day 1; however, at the investigator's discretion the discharge may be delayed to Day 2 for medical or logistical reasons. A minimum washout period of 3 days is required between each dosing period. During the washout period, patients will transition to their normal insulin treatment with guidance from the investigator. The maximum duration allowed for both study periods is 5 weeks.

More information on the clamp methodology can be found in Section 9.6.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to 42 patients may be enrolled so that approximately 34 patients complete the study. For purposes of this study, a patient completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) are finished.

If patients discontinue the study before completion of both clamp periods, replacement patients may be enrolled up to 42 patients following agreement between the investigator and the sponsor. The replacement patients will be assigned the treatment sequence of the discontinued patient and complete that 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 minimise potential bias. The Lilly clinical pharmacologist (CP)/Lilly study team will be unblinded.

A euglycaemic 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 for a detailed description of the clamp methodology.

Patients with T2DM were selected based on the need to conduct PK, GD and safety assessments of LY900014 as part of our intended population.

Based on the PK properties of treprostinil (half-life associated with the terminal rate constant in non-compartmental analysis [$t_{1/2}$] = approximately 1 hour) and Humalog ($t_{1/2}$ = approximately 0.7 hours), a minimum of 3 days for the washout period between study dosing for each consecutive study periods and at least 14 days between the last dose of study drug and the follow-up visit 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, and in patients with T1DM using MDI or insulin pump treatment and T2DM using MDI. In an MDI regimen, the total daily insulin dose is divided into approximately 50% delivered as the basal insulin dose and the other 50% divided among preprandial insulin doses. In this patient population, the weight-based total daily insulin dose for a large majority of patients is 0.6 to 1.2 U/kg/day, although some highly insulin-resistant patients may require more than 2.0 U/kg/day (Rosenstock et al. 2008). It is estimated that the body weight would be around 100 kg making the total daily prandial dose between 30 and 60 U/day or 10 to 20 U for 3 daily meals. Thus, the 15 U dose of LY900014 within this study would delivery approximately a 0.15 U/kg dose and would not exceed this high estimate for the total daily preprandial insulin.

CCI [redacted]

6. Study Population

Eligibility of patients for study enrolment 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 enrolment. 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 enrolment criteria, also known as protocol waivers or exemptions, is 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 enrolment:

[1] are male or female patients with T2DM for at least 1 year.

[1a] male patients:

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

[1b] female patients:

A. Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.

B. Otherwise, women of childbearing potential participating must agree to use 1 highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception for the entirety of the study.

a. Women of childbearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

b. Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) will be used. The patient may choose to use a double-barrier method of

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

C. women not of childbearing potential may participate and include those who are:

   a. infertile due to surgical sterilisation (hysterectomy, bilateral oophorectomy or tubal ligation), congenital anomaly such as mullerian agenesis; or

   b. post-menopausal – defined as either

      1. A woman aged less than 52 years; and being amenorrhoeic for more than 1 year with a serum follicle-stimulating hormone (FSH) level compatible with postmenopausal status; or

      2. Aged at least 52 years and being amenorrhoeic for at least 1 year with a FSH level compatible with post-menopausal status; or

      3. Aged at least 52 years and being amenorrhoeic for more than 1 year

[2] are aged 18 to 70 years at the time of screening.

[3] have a body mass index of 18.5 to 35.0 kg/m^2, inclusive, at screening.

[4] have venous access sufficient to allow for glucose infusion and blood sampling procedures as per protocol.

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

[6] are able and willing to give signed informed consent approved by Lilly and the ethical review board (ERB) governing the site.

[7] 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.

[8] have a glycated haemoglobin (HbA_1c) <9.0% at screening.

[9] have had no episodes of severe hypoglycaemia in the past 6 months (see Section 9.4.5.3).

[10] are on stable prandial insulin, plus/minus basal insulin (neutral protamine Hagedorn [NPH] insulin, insulin glargine or insulin detemir) with or without a stable dose of metformin, DDP-IV inhibitors, sulphonylureas and SGLT-2 inhibitors, for at least 3 months before screening. See Section 5.1 for OAD washout details.

[11] have a fasting C-peptide ≤1.0 nmol/L. Patients who had C-peptide levels >1.0 nmol/L may be re-tested once. If the re-test yields a C-peptide ≤1.0 nmol/L, then the patient satisfies this criterion.

6.2. Exclusion Criteria

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

[12] 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.

[13] are Lilly employees or employees of the investigational site/CRU.

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

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

[16] have previously completed or withdrawn from this study.

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

[18] have a supine blood pressure at screening outside the range of 90 to 160 mmHg for systolic or 50 to 95 mmHg for diastolic (1 repeat is allowed) as determined by the investigator, or results with unacceptable deviations that are judged by the investigator to be clinically significant for the population, or have a heart rate outside the range of 50 to 90 beats/minute.

[19] have donated blood of more than 450 mL or more in the past 3 months or provided any blood donation within the past 1 month before screening.

[20] have a history or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine (apart from T2DM), haematological or neurological disorders capable of significantly altering the absorption, metabolism or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data.

[21] have known or ongoing psychiatric disorders.

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

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

[24] 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 (1 unit of alcohol is defined as 10 mL [8 g] of pure alcohol).

[25] are unwilling to comply with the dietary requirements/restrictions during the study: (i) comply with the fasting requirements of the study, (ii) consume only the meals/snacks provided during the inpatient visits.

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

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

[28] 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).

[29] 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).

[30] are women who are pregnant or lactating.

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

[32] have a history of renal impairment (exclusion only if estimated glomerular filtration rate [estimated GFR] <60 mL/minute/1.73 m^2 [GFR is estimated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine equation]), or have a serum creatinine level ≥0.000126 mol/L (male) or ≥0.000111 mol/L (female).

[33] 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 judged by the investigator.

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

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

[36] 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 hyperglycaemia or insulin resistance or that promote weight loss within 14 days before dosing (apart from vitamin/mineral supplements, occasional acetaminophen [paracetamol] or ibuprofen).

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

[38] any significant changes in insulin regimen and/or unstable blood glucose control within the past 3 months prior to screening as assessed by the investigator.

[39] require daily insulin treatment ≥1.2 U/kg/body weight.

[40] are treated with a CSII (insulin pump).

[41] currently receiving insulin degludec therapy or insulin degludec combinations, or have been treated with degludec within the past 30 days.

[42] currently receiving dulaglutide therapy or have been treated with dulaglutide within the past 30 days.

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

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 fast for approximately 8 hours prior to dosing until after the glucose clamp procedure is completed, after which patients will receive a meal. Water can be consumed freely during this time. 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. Patients will take their regular prandial insulin with the end-of-study meal and site will record the dose and time in the patients eCRF.

When not a resident at the CRU, patients will be encouraged to follow their normal diets.

6.3.2. Caffeine, Alcohol and Tobacco

No alcohol will be allowed at least 24 hours before each dose and throughout the duration of each CRU visit. Between dosing visits, daily alcohol should not exceed 3 U for males and 1.5 U for females (a unit is defined in Exclusion Criterion [24]).

Patients should refrain from caffeine-containing food/beverages (for example, cola, chocolate, tea and coffee) for at least 12 hours before each dose and throughout the duration of each CRU visit.

Smoking (cigars, cigarettes or pipes) and the use of smokeless tobacco will not be permitted during the study.

6.3.3. Activity

Patients are encouraged to maintain their regular exercise habits; however, they should not undertake vigorous or prolonged exercise within 48 hours prior to each dosing day. After dosing, patients should remain recumbent or sitting in the CRU until the end of the glucose clamp.

Movement will be restricted to retain the integrity of connections to the infusion(s) and the study procedures.

6.3.4. Washout Period

During the insulin-transition and wash-out period hyperglycaemia will be monitored daily by fasting fingerstick blood glucose measured and documented in a diary. Each patient will be instructed to contact the investigational site staff if his/her fasting fingerstick glucose level is >240 mg/dL. The patient will be managed as considered appropriate by the Investigator based on the actual glucose value (e.g., return to the study center for evaluation). If the patient has a fasting fingerstick glucose level >240 mg/dL on two consecutive days, the patient will be instructed to return to the study center the following day to have a fasting plasma glucose performed. If the fasting plasma glucose >240 mg/dL is confirmed, the patient will be withdrawn from the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study may be rescreened 1 time. Individuals who still do not meet participation criteria after rescreening (screen failure) may not be rescreened.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of 15 U LY900014 and 15 U Humalog each administered once through SC injection. Table ITRU.2 shows the treatment regimens.

Table ITRU.2. Treatments Administered

Regimen	Dose Strength	Dose Administration	Route of Administration
LY900014	100 U/mL	15 U	Subcutaneous
Humalog	100 U/mL	15 U	Subcutaneous

The investigator or designee is responsible for

- explaining the correct use of the IP(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensation and collection, and
- returning all unused medications to Lilly or its designee at the end of the study

Note: 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 trial materials.

7.1.1. Packaging and Labelling

Clinical trial materials will be labelled according to the country's regulatory requirements. LY900014 will be supplied by Lilly or its representative in accordance with current good manufacturing practices and will be supplied with lot numbers. Humalog (commercially available) will be supplied by Lilly.

The study insulin will be provided to the site unblinded. CCI [redacted] An unblinded pharmacist at the site or other site personnel who are unblinded will use the insulin vials provided to prepare the blinded syringes.

7.2. Method of Treatment Assignment

The treatment to be injected on a given treatment day will be determined according to a randomisation schedule.

7.2.1. Selection and Timing of Doses

The actual date and time of all dose preparation 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 aim is to administer study doses at approximately the same time on Day 1 of each study period.

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

The site of administration of each injection will be recorded. The insulin used in this study will be injected using syringes and vials. Injection sites selected should be about 5 cm from the umbilicus. The same size syringe/needle combination will be used for all patients across periods and will ensure consistent injection depth into the SC space. Injections will be rotated among different injection sites on the anterior abdominal wall during the 2 study periods (that is, left lower quadrant and right lower quadrant).

7.3. Blinding

This is a patient- and investigator-blind study. The Lilly CP/Lilly study team will be unblinded.

Emergency codes will be available to the investigator. A pharmacist or other site personnel who is unblinded will be required to prepare the insulin doses for administration. A code that reveals the treatment group for a specific study patient may be opened during the study only if the patient's well-being requires knowledge of the patient's treatment assignment. The site personnel who performs the drug administration will not be blinded and will be separate and distinct from those who are involved in patient care and patient assessments.

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 adjustments are not allowed in this study.

7.5. Preparation/Handling/Storage/Accountability

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

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

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

7.6. Treatment Compliance

The study drugs 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(s) at the time of study entry should continue their regular, unchanged dose throughout the study (including metformin). Patients receiving multiple daily insulin injections will discontinue their basal and prandial insulin regimens as described in the study design, prior to receiving study treatment (Section 5.1). Additionally, patients receiving OAD will discontinue use (with the exception of metformin) according to guidance in Section 5.1. Similarly, where applicable the patient's insulin regimen should resume in between dosing periods and 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, anti-hypertensive medication, lipid-lowering agent, thyroid hormone replacement medication, hormonal contraceptives 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

Humalog and LY900014 will not be made available to patients after the conclusion of the study. Patients will resume their previous insulin regimen after the study procedure has been completed.

8. Discontinuation Criteria

Patients discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per the Schedule of Activities (Section 2) of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the IP for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- ALT (alanine aminotransferase) AST (aspartate aminotransferase) > 8X for patients ULN (upper limit of normal)
- ALT or AST > 5X ULN for patients sustained for more than 2 weeks or
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or INR >1.5 or
- ALT or AST >3X ULN the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the Sponsor or investigator identifies a patient who did not meet enrolment criteria and was inadvertently enrolled, the patient must be discontinued from the study.

8.2. Discontinuation from the Study

Patients will be discontinued under the following circumstances:

- Enrolment in any other clinical study involving an IP or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
    - Participation in the study needs to be stopped for safety reasons in the case of a severe hypoglycaemic episode (see Section 9.4.5.3)

- Patient Decision
    - the patient, or legal representative, requests to be withdrawn from the study.

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

8.3. Patients Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

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

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

Appendix 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

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 IP or the study, or that caused the patient to discontinue the IP before completing the study. The investigator remains responsible for following AEs through an appropriate health care option. All AEs will be followed until restoration or until a stable condition has been achieved. The follow-up should not be interrupted, even if there is a reasonable explanation for the event.

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 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 IP, 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.

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

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalisation
- 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 hospitalisation but may jeopardise the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly clinical research physician (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.

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 CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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 IP. However, if an SAE occurs after signing informed consent, but prior to receiving IP, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

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

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 IP 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 IPs 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 IP 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 15 U.

Excess insulin administration may cause hypoglycaemia and hypokalaemia. Mild episodes of hypoglycaemia usually can 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 hypoglycaemia may recur after apparent clinical recovery. Hypokalaemia must be corrected appropriately.

The glucose clamp procedure is an inpatient procedure, and hence patients will be continuously monitored. As such, hypoglycaemia can be assessed and treated quickly by trained site personnel.

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).

9.4.2. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2).

Blood pressure and pulse rate should be measured after at least 10 minutes supine.

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

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

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

9.4.3. Electrocardiograms

For each patient, 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 IP, 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 according to the Schedule of Activities (Section 2).

Electrocardiograms must be recorded before collecting any blood samples. Patients must be supine for approximately 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. 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/corrected QT interval from baseline) after enrolment, the investigator will determine if the patient can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Physical Examinations

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

9.4.4.1. Body Weight

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

9.4.4.2. Hip and Waist Circumference

Hip and waist circumference will be recorded as specified in the Schedule of Activities (Section 2). The average of triplicate measurements of waist (narrowest circumference between lowest aspect of the ribs and anterior superior iliac crests) and the hip (widest circumference between the anterior superior iliac crests and the greater trochanters) circumference will be measured.

9.4.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- adverse events

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

9.4.5.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase and creatinine 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 ≥5X ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.4.5.2. Glucose Monitoring

Hypoglycaemia will be described using the following definitions:

- **Documented Glucose Alert Level (Level 1), Plasma Glucose ≤70 mg/dL (3.9 mmol/L):**
  - **Symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by plasma glucose ≤70 mg/dL (3.9 mmol/L)
  - **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with plasma glucose ≤70 mg/dL (3.9 mmol/L)
    - **Unspecified hypoglycaemia:** an event during which plasma glucose ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded
- **Documented Clinically Significant Hypoglycaemia (Level 2) PG <54 mg/dL (3.0 mmol/L)**
  - **Symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by plasma glucose ≤54 mg/dL (3.0 mmol/L)

  - **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with plasma glucose ≤54 mg/dL (3.0 mmol/L)
    - **Unspecified hypoglycaemia:** an event during which plasma glucose ≤54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded
- **Severe hypoglycaemia (Level 3):** an event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. During these episodes, the patient has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (plasma glucose ≤70 mg/dL [3.9 mmol/L])
  - **Severe hypoglycaemia requiring medical attention:** a severe hypoglycaemic event when patients require therapy by health care physicians, emergency medical technicians, emergency room personnel, etc.)

Other Hypoglycaemia:

- **Nocturnal hypoglycaemia:** any hypoglycaemic event (documented symptomatic, asymptomatic, probable symptomatic or severe hypoglycaemia) that occurs between bedtime and waking
- **Relative hypoglycaemia:** an event during which typical symptoms of hypoglycaemia, that do not require the assistance of another person, are accompanied by plasma glucose >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold
- **Overall (or total) hypoglycaemia:** This optional category combines all cases of hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, the event is counted only once in this category

Probable symptomatic hypoglycaemia: An event during which symptoms of hypoglycaemia are not accompanied by a plasma glucose measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

The goal of the euglycaemic clamp is to maintain glucose concentrations at normoglycaemic levels close to a predefined target. Therefore, during a euglycaemic clamp, asymptomatic plasma glucose readings of ≤70 mg/dL will not be recorded as a hypoglycaemic event, unless deemed clinically significant by the investigator or if related to technical issues experienced during the euglycaemic clamp.

9.4.5.3. Severe Hypoglycaemia

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

Only severe hypoglycaemic episodes will be reported as AEs. All episodes of severe hypoglycaemia will be reported as SAEs.

9.4.6. Injection-Site Assessments (Local Tolerability)

Injection-site assessments for local tolerability will be conducted as specified in the Schedule of Activities (Section 2) and more frequently if deemed necessary by the investigator.

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

Local tolerability at the injection site will be evaluated by means of assessments within the following categories: pain on palpation, itching, erythema, oedema and induration/infiltration.

9.4.6.1. Pain Measurements using the Visual Analogue Scale

Pain measurements will be assessed using the electronic version of the 100-mm validated visual analogue scale (VAS) (or electronic VAS [eVAS]) for pain. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection-site pain. The eVAS 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 electronically to indicate pain intensity associated with each injection at time points 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 well-being of the patient. Analgesia can be prescribed in response to pain and must be documented in the concomitant medication section of the eCRF.

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 serum concentrations of insulin lispro. 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

Samples will be analysed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Serum concentrations of insulin lispro will be measured using a validated enzyme-linked immunosorbent assay method specific for insulin lispro at a laboratory approved by the sponsor. Serum remaining may be used for other analyses on insulin lispro.

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

9.6. Glucodynamics (Euglycaemic Glucose Clamp)

The aim of the euglycaemic glucose clamp is to maintain target glucose levels through infusion of a 20% D-glucose (dextrose) solution after the administration of a dose of insulin. During the glucose clamp, the glucose infusion rate (GIR) will be adjusted to maintain a predetermined target blood glucose concentration for the individual patient. Thus, blood glucose concentrations are kept constant while the GIR varies. The varying GIR will then reflect the GD activity of insulin.

Patients with T2DM will participate in euglycaemic glucose clamps on 2 separate visits. All glucose clamp procedures will be performed following an overnight fast of at least 8 hours. On the morning of each study period, 3 IV catheters will be inserted as follows:

- For sampling of arterialised venous blood for the clamp device's blood glucose measurements, a hand or forearm vein of 1 arm will be cannulated. This hand will remain under a heating pad throughout the clamp procedure. The heating of the hand results in an arterialisation of the venous blood due to a reflexive opening of arterio-venous shunts (McGuire et al. 1976; Liu et al. 1992). A low-dose heparin solution (10,000 U/100 mL saline) will be infused via a double lumen catheter. The heparin solution will be taken up together with blood used for the blood glucose measurement in the other lumen of the catheter and helps to prevent blood clotting in the system.
- A catheter will be inserted into the same arm for obtaining blood samples. This cannula will be kept open by use of a mandrin/stylet.
- A forearm vein of the contralateral arm will be cannulated with an 18-gauge polyetrafluoroethylene catheter for the clamp device's controlled variable glucose infusion and for the infusion of insulin glulisine, if needed during the run-in period.

Approximately 1 to 6 hours before the planned administration of study drug, patients will be connected to the clamp device 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 5.5 mmol/L (100 mg/dL) ±20% (upper and lower limits included) must be kept at -60 to -30 minutes before study drug administration. Subsequently, the target blood glucose level of 5.5 mmol/L (100 mg/dL) ±10% (upper and lower limits included) must be kept at -30 to 0 minutes before trial product administration. The blood glucose level must not exceed each target range for more than 5 min (for each of the two 30-minute periods), otherwise the run-in period should be adequately extended in order to fulfil the target ranges. The IV insulin 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 infusion should be stopped at least 30 minutes prior to dosing. Baseline is defined as the mean of blood glucose concentrations at –6, –4 and –2 minutes before trial product administration as measured using CCI, and the onset of action occurs when blood glucose drops to 0.3 mmol/L (5 mg/dL) below baseline. If there are no stable blood glucose measurements using 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 within 6 hours after starting the run-in period, 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 (5.5 mmol/L; 100 mg/dL). The GIR necessary to keep the blood glucose concentration at the target level will be recorded every minute throughout the glucose clamp. At least every 30 minutes throughout the glucose clamp, blood glucose will be performed using CCI Repeat samples for counter-checking of apparent spurious results may be taken where indicated.

The clamp procedure will continue for approximately 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 and after end of sampling, 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.

The sample(s) will be stored for up to a maximum of 1 year after the last patient visit for the study at a facility selected by the sponsor.

9.7. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production to 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 anti-drug antibodies in the presence of insulin lispro. 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.

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

9.8. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, 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 IP and to investigate genetic variants thought to play a role in diabetes mellitus and related complications. 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/IRBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions and investigation of variable response that may not be observed until later in the development of LY900014 or after LY900014 is commercially available.

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

9.9. Exploratory Biomarkers

9.9.1. C-Peptide

Blood samples (2.5 mL) will be collected to determine serum concentrations of C-peptide as described in the Schedule of Activities (Section 2) using a validated method at a central laboratory. These samples and any remaining serum after C-peptide analyses will be discarded. Instructions for the collection and handling of these samples will be provided by the sponsor.

9.10. Health Economics

Not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 42 patients may be enrolled to ensure that at least 34 patients complete the study. Thirty-four completing patients will provide approximately 95% 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[0-30min]) between LY900014 and Humalog. Testing will be done at alpha-level of 0.05 with a 2-sided 95% confidence interval (CI). The variability was estimated by analysing Lilly internal studies that showed an average log-scale standard deviation of within-patient difference in AUC(0-30min) of 0.5. Analysis of internal data showed a log-scale standard deviation of within-patient difference in time to early half-maximal drug 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 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 80% power to detect a 20% decrease in both time to onset of insulin action (t_{onset}) and time to half-maximal GIR before tR_{max} (early 50% tR_{max}) and approximately 85% power to detect at least a 40% increase in total amount of glucose infused (Gtot) over 30 minutes ($Gtot_{[0\text{-}30min]}$) and Gtot over 1 hour ($Gtot_{[0\text{-}1h]}$).

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, height, weight, body mass index, race/subrace or other demographic characteristics will be recorded.

10.3. Statistical Analyses

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

Pharmacokinetic/pharmacodynamic analyses will be conducted on data from all patients who receive at least 1 dose of the study drug and have evaluable PK.

Primary statistical analyses will be conducted on the set of patients who complete at least the first period of treatment. Supportive analyses will be done on the key parameters for the patients who complete all treatment periods. Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis

methods described in the protocol and the justification for making the change will be described in the study results.

Additional exploratory analyses of the data 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 IP and protocol-procedure AEs will be listed; if the frequency of events allows, safety data will be summarised using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with IP as perceived by the investigator. Symptoms reported to occur prior to study entry/enrolment 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 Dictionary for Regulatory Activities.

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

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

10.3.1.3. Statistical Evaluation of the Intensity of Injection-Site Pain

Pain intensity will be assessed at each injection site immediately after the injection as reported by the patient and measured according to the 0- to 100-mm VAS.

A mixed-effect model will be used to analyse the time 0 (immediately after dosing) data using the statistical model that includes treatment, sequence and period as fixed effects; and patient within sequence as a random effect. The distribution of the score data will be explored prior to analysis to determine whether data transformation is required. It is possible that VAS scores will be 0; hence if the distribution of the data implies that a log transformation is required, then the score may be updated to log (VAS+1) to allow for the inclusion of the 0 values in the analysis.

Visual analogue scale data will also be summarised based on the following categories of score: 0, 1 to 10, 11 to 20, 21 to 30, 31 to 40, etc., up to the maximum category by treatment and 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.

Pharmacokinetic 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 used 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 drug concentration (late 50% t_{max}), maximum observed drug concentration (C_{max}), time to maximum observed drug concentration (t_{max}), half-life ($t_{1/2}$), AUC from time zero to the last recorded time [AUC(0-tlast)], AUC from time zero to 30 minutes [AUC(0-30min)], AUC from time zero to 1 hour[AUC(0-1h)], AUC from time zero to 10 hours [AUC(0-10h)], AUC from time 3 to 10 hours (AUC[3-10h]) and AUC from time zero to infinity [AUC(0-∞)]. In addition, the apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and volume of distribution after extra-vascular administration (Vz/F) also will be determined. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary, such as AUC from time zero to 2 hours [AUC(0-2h)].

The insulin lispro PK parameters for assessing faster insulin lispro absorption are the early 50% t_{max} and AUC(0-30min).

The insulin lispro PK parameters for assessing reduction in the late insulin lispro exposure are the late 50% t_{max} and AUC(3-10h).

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

10.3.2.2. Pharmacokinetic Statistical Inference

Log-transformed PK parameters 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.

10.3.3. Glucodynamic Analyses

10.3.3.1. Glucodynamic Parameter Estimation

Glucodynamic assessments will be determined from the glucose 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 The fitted data for each patient will be used to calculate the following GD parameters: T_{onset}, maximum GIR (R_{max}), time to R_{max} (tR_{max}), time to half-maximal GIR before tR_{max} (early 50% tR_{max}), time to half-maximal GIR after tR_{max} (late 50% tR_{max}), total amount of glucose infused over the duration of the clamp (Gtot), total amount of glucose infused over 30 minutes ($G_{tot[0\text{-}30min]}$), and total amount of glucose infused over 1 hour ($G_{tot[0\text{-}1h]}$). Additional partial glucose AUCs, such as total amount of glucose infused over 2 hours ($G_{tot[0\text{-}2h]}$), and total amount of glucose infused from 3 hours to 10 hours $G_{tot[3\text{-}10h]}$ may be computed, as necessary. The values of these GD parameters will be summarised by treatment and/or period through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated. The primary GD parameters for earlier PD onset are early 50% tR_{max}, $G_{tot(0\text{-}30min)}$, $G_{tot(0\text{-}1h)}$, and T_{onset}.

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 G_{tot} over 2 hours ($G_{tot[0\text{-}2h]}$), and G_{tot} from 3 hours to 10 hours $G_{tot[3\text{-}10h]}$ 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.

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}, 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.

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 GD data for both study periods.

10.3.4. Evaluation of Immunogenicity

The frequency of antibody formation to insulin lispro will be determined. The relationship between the presence (or absence) of antibodies and AEs will be assessed. Likewise, the

relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may be assessed.

10.3.5. C-Peptide

Mean and individual C-peptide concentration versus time plots with both treatments will be presented. In addition, individual plots overlaying the C-peptide concentration versus time with the insulin lispro serum concentration versus time will be presented. Other plots that may be explored include the C-peptide concentrations relative to the GIR, and/or blood glucose concentrations during the euglycaemic clamp.

10.3.6. 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.

The Lilly CP/Lilly study team is unblinded. Data may be analysed while the trial is ongoing, but no changes to the study design are planned. The results may help Lilly expedite final delivery and enable planning of future studies. An assessment committee will not be formed.

11. References

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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 unfavourable 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
assent	greement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-30min)	area under the concentration versus time curve from time zero to 30 minutes
AUC(0-1h)	area under the concentration versus time curve from time zero to 1 hour
AUC(0-2h)	area under the concentration versus time curve from time zero to 1 hour
AUC(0-10h)	area under the concentration versus time curve from time zero to 10 hours
AUC(3-10h)	area under the concentration versus time curve from 3 to 10 hours
AUC(0-tlast)	area under the concentration versus time curve from time zero to the last recorded time
AUC(0-∞)	area under the concentration versus time curve from time zero infinity
BG	blood glucose
blinding	a procedure in which 1 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
CI	confidence interval
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	maximum observed drug 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 re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSII	continuous subcutaneous insulin infusion
DPP-IV	dipeptidyl peptidase IV inhibitor
early 50% t_{max}	time to early half-maximal drug concentration
early 50% tR_{max}	time to half-maximal GIR before tR_{max}
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
eVAS	electronic visual analogue scale
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	good clinical practice
GD	glucodynamics
GFR	glomerular filtration rate
GIR	glucose infusion rate
Gtot	total amount of glucose infused

$Gtot_{(0\text{-}30min)}$	total amount of glucose infused over 30 minutes
$Gtot_{(0\text{-}1h)}$	total amount of glucose infused over 1 hour
$Gtot_{(0\text{-}2h)}$	total amount of glucose infused over 2 hours
$Gtot_{(3\text{-}10h)}$	total amount of glucose infused from 3 to 10 hours
HIV	human immunodeficiency virus
IB	investigator's Brochure
ICF	informed consent form
ICH	international Council for Harmonisation
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.
investigational product (IP)	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 authorised form, or marketed products used for an unauthorised indication, or marketed products used to gain further information about the authorised 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 drug concentration
late 50% tR_{max}	time to half-maximal GIR after tR_{max}
legal representative	an individual or judicial or other body authorised under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
LOESS	locally weighted scatterplot smoothing
MDI	multiple daily injection
non-investigational product (non-IP)	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
OAD	oral antidiabetic medication
PAH	pulmonary arterial hypertension

PK	pharmacokinetic(s)
randomise	the process of assigning patients to an experimental group on a random basis.
R_{max}	maximum GIR
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.
SGLT-2	sodium-glucose co-transporter-2
SMPG	self-monitoring plasma glucose
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life associated with the terminal rate constant in non-compartmental analysis
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
t_{max}	time to maximum observed drug concentration
t_{onset}	time to onset of insulin action
tR_{max}	time to R_{max}
Vz/F	volume of distribution after extra-vascular administration
ULN	upper limit of normal
VAS	visual analogue scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Haematology[a]	Clinical Chemistry[a]
Haematocrit	Sodium
Haemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell haemoglobin	Calcium
Mean cell haemoglobin concentration	Phosphorus
Leucocytes (WBC)	Glucose, fasting
Absolute counts of	Blood urea nitrogen (BUN)
Neutrophils	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Total protein
Eosinophils	Albumin
Platelets	Total bilirubin
Basophils	Alkaline phosphatase (ALP)
HbA1c[b]	Aspartate aminotransferase (AST)
Urinalysis	Alanine aminotransferase (ALT)
Specific gravity	Creatinine
pH	Gamma-glutamyl transferase (GGT)
Protein	
Glucose	
Ketones	Breath ethanol testing[b,c]
Bilirubin	Urine drug screen[b,c]
Urobilinogen	Hepatitis B surface antigen[b]
Erythrocytes/haemoglobin	Hepatitis C antibody[b]
Nitrite	HIV[b]
Leucocytes	Pregnancy test[d]
Microscopy[e]	FSH[b]
Coagulation[b]	
Prothrombin time (PT)	
Partial thromboplastin time (PTT)	

Abbreviations: FSH = follicle-stimulating hormone; HbA1c = glycated haemoglobin; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

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

b Performed at screening only.

c May be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.

d Females only: serum pregnancy test at screening, urine pregnancy test as indicated by the Schedule of Activities.

e If clinically indicated, per investigator's discretion.

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 or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Study-specific recruitment material should be approved by Lilly.

Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

- the current IB 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 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 organisation.

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 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 CRP.

Hepatic Monitoring Tests

Hepatic Haematology[a]	**Haptoglobin[a]**
Haemoglobin	
Haematocrit	**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 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**
CPK	**Antibody)[a]**

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

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

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

Appendix 5. Blood Sampling Summary

This table summarises the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories and bioanalytical assays) during the study.

Protocol I8B-MC-ITRU Sampling Summary

Purpose	Blood Volume per Sample(s) (mL)	Number of Blood Samples	Total Volume (mL)
Screening[a]	11	1	11
Clinical laboratory tests[a]	11	2	22
Pharmacokinetics – insulin lispro	2.5	25 samples × 2 periods = 50	125
Pharmacodynamics – C-peptide	2.5	12 samples × 2 periods = 24	60
Immunogenicity	5	3	15
Pharmacogenetics	10	1	10
Clamp device sampling for glucose[b]	NA	NA	64
Blood glucose during clamp period (Super GL)[c]	0.3	64	19.2
Total			326.2
Total for clinical purposes			330

Abbreviation: NA = not applicable.

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

[b] Clamp device sampling: 6-hour run-in plus 10-hour clamp = 16 hours × 2 periods = 32 hours × 2 mL/hour = 64 mL.

[c] Blood glucose during clamp period (Super GL): 6-hour run-in plus 10-hour clamp = 16 hours × 2 samples/hour = 32 blood samples × 0.3 mL/blood sample = 9.6 mL × 2 periods = 19.2 mL.

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