Protocol: I8B-MC-ITRV(b)
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared

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Protocol I8B-MC-ITRV(b)
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog® in Patients with T1DM

EUDRACT: 2017-001500-30

Confidential Information

LY900014

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1. Protocol Synopsis

Title of Study:
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog in Patients with T1DM

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 mimic the physiological prandial insulin secretion pattern, which may more effectively, control postprandial glucose excursions and allow increased flexibility of the time of dosing relative to a meal.

The aim of this study is to compare the insulin lispro pharmacokinetic (PK), glucodynamic (GD), and tolerability profiles of insulin lispro following administration of either LY900014 or Humalog during a mixed meal tolerance test (MMTT) in patients with T1DM.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
1. To evaluate the PK of insulin lispro following a single SC injection of LY900014 and Humalog in patients with T1DM	1. Early 50% t_{max} and AUC(0-30min)
Secondary	
1. To evaluate the effect of injection-to-meal timings (immediately before the start of meal, and 20 minutes following the start of the meal) on the GD response to LY900014 compared to Humalog, as measured by the MMTT	1. ΔAUC(0-2h), ΔAUC(0-5h)
2. To evaluate the tolerability of LY900014	2. AEs and hypoglycemic events

Abbreviations: AE = adverse event; AUC(0-30min) = area under the concentration versus time curve (AUC) from time zero to 30 minutes; ΔAUC = area under the baseline subtracted glucose concentration versus time curve; early 50% tmax = time to early half-maximal drug concentration; GD = glucodynamics; MMTT = mixed meal tolerance test; PK = pharmacokinetics; SC = subcutaneous; T1DM = type 1 diabetes mellitus

Summary of Study Design:

Study I8B-MC-ITRV is a Phase 1, randomized, patient and investigator blind, 2-treatment, 4-period crossover study to evaluate meal to dose-timing in patients with T1DM.

Treatment Arms and Planned Duration for an Individual patient:
Patients will be screened over a 14 day period prior to start of an approximate 2-week lead-in/insulin transition period. Patients will then participate in a dose-finding assessment (Day -1 of Period 1) and subsequently

randomised to 1 of 4 treatment sequences according to the actual randomization table provided to the site. In each study period, patients will undergo an MMTT. Each patient will receive a single subcutaneous injection of either LY900014 or Humalog either immediately before the test meal or 20 minutes following the start of the test meal. All treatment procedures will be inpatient stays of approximately 2 days per period and require a maximum of 6 weeks to complete 4 periods. Each study dosing will be separated by a minimum of 21 hours and may occur on consecutive visits, however patient inclusion is subject to required screening criteria. The follow-up or early discontinuation visit should occur at least 14 days after the last dose of the study drug.

Treatment:

LY900014: Single individualized SC dose per assessment period

Humalog: Single individualized SC dose per assessment period

Number of Patients:
Up to 36 patients may be enrolled to ensure that at least 30 patients will complete the study. Thirty completing patients will provide greater than 95% power to demonstrate a 2-fold increase in the serum insulin lispro AUC(0-30min) between LY900014 and Humalog when both are given immediately before meals.

Statistical Analysis:
Primary statistical analyses of PK and GD parameters will be conducted on the set of patients who complete all treatment periods. Supportive analyses may be done on the key parameters for the patients who complete at least the first period of treatment. Safety analyses will be conducted on the set of patients receiving at least 1 dose of the study drug to which they are randomized, regardless of whether or not they completed all protocol requirements.

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

Safety: All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety parameters will be listed and summarized using standard descriptive statistics.

Pharmacokinetic: Log transformed AUCs, Cmax, CL/F and Vz/F for insulin lispro will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog, and the corresponding 95% CIs of the ratios using the mixed-effects model that includes treatment and period as fixed effects and patient 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 (LSmeans), treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LS means will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

Glucodynamic: Data will be analyzed for the patients during each MMTT. The change from baseline values (the average of -30, -15, and 0 minutes) represented as the 0-hour time point following the start of the MMTT for each patient will be calculated. The area under the baseline subtracted glucose concentration versus time curve from time 0 to 2hr (ΔAUC[0-2h]) and area under the baseline subtracted glucose concentration versus time curve from time 0 to 5hr post meal (ΔAUC[0-5h]) will be calculated. In addition, the change from baseline maximum glucose

observed during the 5 hours postmeal and change from baseline 1 hour glucose and 2 hour glucose post the start of the meal will be calculated. Other partial ΔAUCs may be calculated as deemed appropriate.

Summary statistics will be presented by treatment and by timing of dose (all 4 combinations of treatment and timing of dose). The GD parameters on the original scale will be analyzed using the mixed-effects model that includes treatment, timing of dose, treatment-by-timing of dose interaction, and period as fixed effects and patient as a random effect.

The p-value on the difference between LS means will be used to determine statistical significance and the corresponding 95% CIs for the LS Mean ratios from Fieller's theorem will be presented.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITRV

	Sign Informed Consent	Screening	Lead-in	Study Period (Periods 1 to 4)		Follow-up/Early discontinuation	Comments
Procedure		Days -30 to -17	14 days prior to Day -2	Day -1	Day 1	≥ 14 days after discharge	
Informed Consent	X						At least 1 day before screening procedures. Screening procedures should take place no later than 28 days after signing the informed consent. (see Section 9.5.2).
Medical History and physical examination		X					
Hip and Waist Circumference				X			Period 1 only
Height		X					At screening only
Weight		X		X			Period 1 only
Vital signs: blood pressure and pulse rate		X			Predose, 30 and 120 minutes postdose	X	Vital signs will be taken while patients are supine at screening and semi-supine on Day 1.
12-lead ECG		X			Predose (Period 1)	X	Single ECGs will be collected for safety.
Clinical laboratory tests		X			Predose for Period 1 only	X	Fasting laboratory test for screening and follow-up. Screening laboratory tests will be analyzed at a local laboratory (see Section 9.5.2).

	Sign Informed Consent	Screening	Lead-in	Study Period (Periods 1 to 4)		Follow-up/Early discontinuation	Comments
Procedure		Days -30 to -17	14 days prior to Day -2	Day -1	Day 1	≥ 14 days after discharge	
Lead-in/insulin transition activities			X (Period 1 only)				Once patients have completed screening procedures, they will switch from prescribed short-acting and basal insulin to site-provided Humalog and insulin glargine respectively. Patients receive general diabetes training. A patient diary will be provided for recording dosing and other required information (Section 9.2.1) Lead-in period may be extended by 2 days (e.g., 16 days prior to Day -2) as needed
Patient Admission to CRU				X			Admitted to CRU evening Day -2 or early morning Day -1 (Period 1 only). For Periods 2 – 4, patients may be admitted evening of Day -1.
Dose-finding				X (Period 1 only)			Following insulin transition, patients will undergo dose-finding with Humalog and a test meal. To take place between 07:00 and 11:00. Blood glucose concentrations will be monitored every 20 minutes for 5 hours postmeal (see Section 9.2.2). See Section 6.2.1 for rescheduling.

	Sign Informed Consent	Screening	Lead-in	Study Period (Periods 1 to 4)		Follow-up/Early discontinuation	Comments
Procedure		Days -30 to -17	14 days prior to Day -2	Day -1	Day 1	≥ 14 days after discharge	
Randomization				X			To take place before run-in of Period 1 Day 1
Pregnancy test		X		X		X	Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at admission for Period 1 and at follow-up (see Appendix 2)
Standard dinner				X			Approximately 19:00
Medical Assessment				X	Predose and before discharge from CRU	X	Medical assessment includes medical review and targeted examination, and as appropriate review of concomitant medication, patient diary and MMTT exclusion criteria (see Section 6.2.1)
Glucose stabilization/run-in					X		From approximately 7 hours to 30 minutes before dosing: infusion of glucose (dextrose solution) or insulin glulisine to achieve a target blood glucose concentration of 135 ±15mg/dL (7.5 ±0.8 mmol/L). Blood glucose concentrations will be monitored at a minimum of 30-minute intervals (see Section 9.2.3.1 and 9.7.1.1). See Section 6.2.1 for rescheduling.

	Sign Informed Consent	Screening	Lead-in	Study Period (Periods 1 to 4)		Follow-up and Early discontinuation	Comments
Procedure		Days -30 to -17	14 days prior to Day -2	Day -1	Day 1	≥ 14 days after discharge	
Blood glucose sampling (MMTT)					-30, -15, 0 minutes pre-meal, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300 minutes post-meal		0-minute time point sample to be taken at the start of the meal.
Mixed Meal Tolerance Test (MMTT)					X		Standardized liquid test meal will be administered at approximately 08:00 (with allowance to 11:00) and should be consumed within 15 minutes. (See Section 9.2.3.2). Study periods to be separated by a minimum 21 hour washout
Study drug administration					X		Either immediately before meal or 20 minutes after start of meal according to randomization schedule: Study drug will be administered at approximately the same time on Day 1 of Periods 1-4. There will be at least 21 hours between study doses.
Injection site local tolerability assessments					0, 20, and 60 minutes postdose		Assessments of injection site local tolerability will occur immediately following the injection

	Sign Informed Consent	Screening	Lead-in	Study Period (Periods 1 to 4)		Follow-up and Early discontinuation	Comments
Procedure		Days -30 to -17	14 days prior to Day -2	Day -1	Day 1	≥ 14 days after discharge	
Insulin lispro PK sampling					0 (predose), 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150,180, 240, 300, 360, and 420 minutes postdose		Sampling times are relative to the time of study drug administration in each period
Pharmacogenetics sample					Predose for Period 1 only		Refer to sample collection instructions provided by the sponsor
Immunogenicity sample			Pre-insulin switch		Predose for Periods 1 and 3	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 all study procedures are completed

Study Schedule Protocol I8B-MC-ITRV

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; min = minutes; MMTT = mixed meal tolerance test; PK = pharmacokinetics

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. Injection-site assessments can be done after PK sampling.

3. Introduction

3.1. Study Rationale

A prandial insulin with faster-on and/or faster-off characteristics might reduce glycemic excursions and the incidence of postprandial hypoglycemia compared to currently available fast-acting insulin analogs. 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 and allow increased flexibility of the time of dosing relative to a meal.

This study aims to compare PK and PD profiles as well as the improved action of insulin lispro from LY900014 on the control of postprandial blood glucose in comparison to Humalog in patients with T1DM. The improved action of insulin lispro will be assessed by using standardized mixed-meal tolerance test (MMTTs). Furthermore, this study will explore the postprandial glucose profiles with LY900014 and Humalog injected at two different meal-to-dose time intervals either immediately before or 20 minutes following the start of the test meal, to optimize future use of this investigational medicinal product (IMP).

3.2. Background

The insulin analog 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 units (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 analogs so that they have an even faster onset to better match carbohydrate absorption and also allow greater flexibility in the time of dosing relative to meals.

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 ([redacted]C) 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 ([redacted]C), 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 2006 (AMIS database [WWW]). Sodium citrate, an excipient that speeds insulin absorption (at least 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 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.

To date, LY900014 has been administered to approximately 89 patients with diabetes (60 T1DM and 29 T2DM) across 3 Phase 1b studies and approximately 107 healthy volunteers across these Phase 1 studies. The total insulin lispro exposure was similar between LY900014 and Humalog; however LY900014 demonstrated a faster and earlier insulin lispro absorption compared to Humalog. Additionally, through the use of multiple daily injections of LY900014 for up to 2 weeks in patients with either T1DM or T2DM, it was found that LY900014 was well tolerated. 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 LY900014 formulations compared to those in relation to Humalog. There were no reported cases of severe hypoglycemia. Additionally, there was no reported incidences of local or systemic allergic reactions.

3.3. Benefit/Risk Assessment

This study will not offer any direct benefits to the patients participating in the study. The data from previous studies in healthy patients and patients with T1DM and T2DM have shown that LY900014 was well tolerated and the adverse drug reactions are in keeping with those reported for Humalog.

Potential risks associated with LY900014, derived from the known risks of insulin lispro (Humalog), are hypoglycemia, hypersensitivity reactions (localized allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral edema (Humalog package insert, 2015).

Notably, across all doses in the studies that have evaluated treprostinil (CCI) as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those AEs associated with systemic absorption of treprostinil, as described in the CCI package insert (2014). The exposures of treprostinil in LY900014 in this study are expected to be undetectable compared to those observed in the dose ranges previously explored with SC bolus administration of treprostinil and are expected to be substantially lower than those observed in the treatment of PAH. No known potential risks are associated with the use of small amounts of treprostinil in the LY900014 formulation.

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

The study includes inpatient procedures during which participants will be continuously monitored. Patients will be without food intake from the start of the MMTT to completion of blood collection (approximately 420 minutes) unless required to treat hypoglycemia, (see Section 9.5.6.2 for definition of hypoglycemia and Section 9.5.8 for treatment guidelines). If a patient experiences elevated blood glucose following food intake for more than 1 hour, insulin glulisine will be administered intravenously (see Section 9.5.8 for treatment guidelines). Patients will maintain their basal insulin regimen of site-provided insulin glargine during the entire study

including the MMTT days unless safety issues arise; in this case, the investigator will discuss a change of the basal insulin regimen with the sponsor clinical pharmacologist (CP) and implement this change, if necessary, to prevent any medical problems.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY900014 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table ITRV.1. Objectives and Endpoints

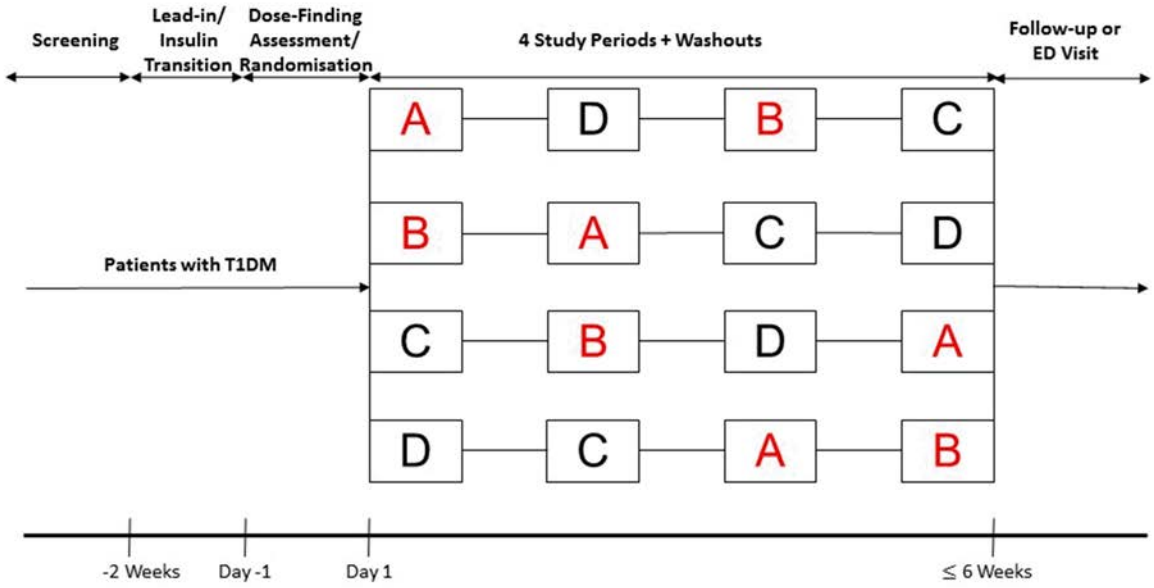
Objectives	Endpoints
Primary	
1. To evaluate the PK of insulin lispro following a single SC injection of LY900014 and Humalog in patients with T1DM	1. Early 50% t_{max} and AUC(0-30min)
Secondary	
1. To evaluate the effect of injection-to-meal timings (immediately before the start of meal, and 20 minutes following the start of the meal) on the GD response to LY900014 compared to Humalog, as measured by the MMTT	1. ΔAUC(0-2hr), ΔAUC(0-5hr)
2. To evaluate the tolerability of LY900014	2. AEs and hypoglycemic events
Exploratory	
1. Explore the formation of anti-drug antibodies to insulin lispro	1. Anti-insulin lispro antibodies

Abbreviations: AE = adverse event; AUC(0-30min) = area under the concentration versus time curve (AUC) from time zero to 30 minutes; ΔAUC = area under the baseline subtracted glucose concentration versus time curve; early 50% tmax = time to early half-maximal drug concentration; GD = glucodynamics; MMTT = mixed meal tolerance test; PK = pharmacokinetics; SC = subcutaneous; T1DM = Type 1 diabetes mellitus.

5. Study Design

5.1. Overall Design

ITRV is a Phase 1, patient- and investigator-blind, randomized, 2-treatment, 4-period crossover study in patients with T1DM to evaluate the insulin lispro PK and GD characteristics of LY900014 compared to Humalog following single SC injections administered at 2 different injection-to-mealtime intervals; either immediately before or 20 minutes following the start of the test meal. Study ITRV may be conducted at 1 or more clinical research units (CRUs).



Treatment	LY900014 or Humalog	Dose Timing Relative to Meal (minute)*
A	LY900014	0
B	LY900014	+20
C	Humalog	0
D	Humalog	+20

* Time 0 is immediately before test meal

Abbreviations: ED = early discontinuation; T1DM = type 1 diabetes mellitus

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

Patients will be required to attend the CRU on at least 8 occasions (no more than 10 occasions if dose-finding and/or one MMTT rescheduled) as noted in the Study Schedule (see Section 2):

- Informed consent
- Screening visit
- Lead-in and insulin transition period (see Section 9.2.1)

- 4 inpatient CRU study visits (including dose finding assessment [see Section 9.2.2])
- A follow-up visit

Eligible patients who have satisfied the entry criteria and completed all screening procedures will return to the CRU at least 2 weeks prior to Period 1 Day -2 to begin a lead-in and insulin transition period. When patients visit the CRU to begin the lead-in period, patients will receive instruction on general diabetes education including measurement of self-monitored plasma glucose (SMPG) and receive instruction on the insulin transition (see Section 9.2.1). During the insulin transition period, patients will transition from their current basal insulin therapy to site-provided insulin glargine and Humalog [redacted] (see Section 9.2.1). Following insulin transition, patients will return to the CRU for the dose-finding assessment (see Section 9.2.2) on either the evening of Day -2, Period 1 or early morning of Day -1, Period 1. The dose-finding assessment will use Humalog administered immediately before a standardized liquid test meal (MMTT) to inform the dose of LY900014 and Humalog to be used during subsequent study MMTT assessments. Upon completion of the dose-finding assessment, patients will be randomised to 1 of 4 treatment sequences. Prior to the MMTT in each study period, patients will undergo a run-in period (see Section 9.2.3.1) to achieve a predetermined glucose target of 135 ±15 mg/dL (7.5 ±0.8 mmol/L). Once the glucose target has been attained, patients will proceed with the MMTT in which a single individualized SC dose of LY900014 or Humalog will be administered either immediately before the test meal or 20 minutes following the start of the test meal (see Section 9.2.3.2).

Doses of LY900014 and Humalog during the 4 study periods will be separated by a minimum washout of approximately 21 hours. The maximum duration allowed for all 4 periods is approximately 6 weeks. Patients will continue using site-provided Humalog and insulin glargine during the washout periods between MMTTs (see Section 7.7 for use of concomitant medication and basal insulin). During the washout periods, patients will be instructed to perform regular blood glucose monitoring (see Section 9.5.7).

Following completion of all study procedures in each Period, patients may be offered a meal and discharged from the CRU at the discretion of the principal investigator.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to 36 patients may be enrolled so that approximately 30 patients complete the study. For purposes of this study, a patient completes the study when all scheduled procedures shown in the Schedule of Activities have been finished. Patients who drop out may be replaced, and the replacement patient will adopt all 4 assigned crossover treatments of the original patient's randomization schedule.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

The study is a 4-period crossover design to reduce the variability of insulin PK and GD, as each patient will act as his/her own control. The total number of patients needed with a crossover design is less than the number needed with a parallel group design. A maximum duration of approximately 6 weeks is allowed for patients to complete all 4 assigned periods to minimize the risk of insulin resistance/changes in mean glycemic control during the study.

Randomization and blinding are used to avoid bias introduced through an association between allocation order of investigational medicinal product (IMP) and patient characteristics. The Lilly clinical pharmacologist (CP)/Lilly study team will be unblinded.

In each study period patients will undergo a run-in period before the MMTT using a variable insulin and glucose IV infusion. This run-in period will allow for improved comparability of the postprandial glucose response to a mixed meal after treatment with LY900014 and Humalog administered either immediately before the start of the meal, or 20 minutes following the start of the test meal. This run-in aims to achieve similar preprandial glucose levels for all patients before the start of the test meal and thereby reduces the variability of the postprandial glucose response. Insulin glulisine has been chosen for the IV optimization of blood glucose during the run-in because insulin glulisine does not cross-react with the insulin lispro–specific assay used for the PK analysis.

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

A minimum of approximately 21 hours washout between the test meals allows for a complete washout of study drug administered with the MMTT and glucose response and prevents carry-over effects.

5.5. Justification for Dose

The bolus dose of insulin lispro (LY900014 or Humalog) will be individualized per patient to cover the carbohydrate content in this standardized liquid test meal. This dose of insulin is reflective of a clinically relevant, individualized insulin dosing, similar to how patients would determine the insulin dose for the carbohydrate content in a meal. For each patient, the individualized prandial insulin lispro dose in LY900014 and Humalog for each test meal must be kept identical throughout the crossover periods.

6. Study Population

Eligibility of patients for study enrollment 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 over a 14 day period prior to the lead-in site visit. Patients who are not entered within this time period, may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

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

a. Male patients:

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

b. Female patients:

i. Women of child-bearing 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.

ii. Otherwise, women of child-bearing potential participating must agree to use one highly effective method of contraception until discharge from final treatment period.

1. Women of child bearing 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 in Period 1.

2. A highly effective method of contraception includes a combined (estrogen and progestogen containing) or progestogen-only hormonal contraception administered orally, intravaginally, or transdermally and is associated with inhibition of ovulation. Alternatively, patients may use either an intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, or the partner should have been vasectomised.

iii. Women not of childbearing potential may participate and include those who are:

1. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy or bilateral salpingectomy), congenital anomaly such as mullerian agenesis; or

2. post-menopausal – defined as a woman being amenorrheic for more than 1 year without an alternative medical cause and a serum follicle-stimulating hormone (FSH) level compatible with postmenopausal status. A FSH level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

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

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

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

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

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

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

[8] have a glycated hemoglobin (HbA_1c) ≤9.0% at screening.

[9] have had no episodes of severe hypoglycaemia in the last 6 months (see Section 9.5.6.3).

[10] are on stable prandial insulin and basal insulin (neutral protamine Hagedorn [NPH] insulin, insulin glargine or insulin detemir) for at least 3 months before screening with a total insulin dose demand of ≤1.5 U/kg/day

6.2. Exclusion Criteria

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

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

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

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

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

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

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

[17] have a supine blood pressure at screening outside the range of 90 to 160 mmHg for systolic or 50 to 100 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.

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

[19] have known or ongoing psychiatric disorders.

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

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

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

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

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

[25] are women who are pregnant or lactating.

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

[27] have a history of renal impairment (exclusion only if 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 ≥126µmol/L (male) or ≥111 µmol/L (female).

[28] 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.

[29] 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.

[30] are currently a smoker as defined as more than 5 cigarettes (or nicotine equivalent) per day.

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

[32] have a significant history of alcoholism or drug abuse as judged by the investigator or consuming more than 24 g of alcohol per day for men, or more than 12 g of alcohol per day for women (1 unit of alcohol is defined as 10 mL [8 g] of pure alcohol).

[33] 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.

[34] 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.

[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 4 weeks before screening.

[36] are treated with a CSII (insulin pump)

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

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

[39] 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.

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

6.2.1. Additional Exclusion Criteria for Inpatient Dosing Days

Patients who fulfil 1 or more inpatient dosing-day exclusion criteria will be excluded from study drug administration for that MMTT day. A single inpatient treatment period can be rescheduled 1 to 14 days later. Each treatment period can only be rescheduled once.

The following exclusion criteria apply to the day ***before*** each MMTT day:

[41] positive drug screen

[42] positive pregnancy test administered on Day -1 of Period 1

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

[44] any use of prescription or non-prescription medication according to Exclusion Criteria [34] and [35]

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

[46] injection of a bolus of more than 6 U of a short-acting insulin (Humalog) between 7 and 12 hours before test meal

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 be fasted (except for water) for at least 10 hours before each test meal and 8 hours prior to screening and follow-up assessments (see Section 9.5.8 for guidelines on hypoglycemia treatment). The patient will not be allowed to consume water for 2 hours after the MMTT assessment begins; however, water may be consumed freely 2 hours postmeal.

While resident in the CRU, patients may not consume any food or caloric drinks other than that provided by the CRU. When not resident in the CRU, patients may resume their regular diet and should not make major changes to the dietary habits during the study.

Following completion of study procedures, patient will be offered a meal. Site will record dose and time of prandial Humalog administered with end-of-study meal.

6.3.2. Caffeine, Alcohol, and Tobacco

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

No alcohol will be allowed at least 24 hours before each CRU admission (Day –1) and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 3 units for males and 2 units for females (see Section 6.2 #32 for unit definition).

No cigarette smoking will be permitted during the study.

6.3.3. Activity

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study may not be rescreened.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY900014 administered by SC injection with Humalog. Table ITRV.2 shows the treatment regimens. Humalog and LY900014 will be provided to site as investigational medicinal products.

Table ITRV.2. Treatments Administered

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

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling of Investigational Medicinal Product

The study insulin will be provided to the site unblinded. The open-label pre-filled pens will contain 3 mL cartridges of either LY900014 (comprising 100 U/mL of insulin lispro and 1000 ng/mL of treprostinil) or Humalog (comprising 100 U/mL of insulin lispro).

During the lead-in/insulin transition period and washout between each MMTT, 100 U/mL Humalog will be provided as open-label pre-filled [redacted]

All clinical study material provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained.

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

7.2. Method of Treatment Assignment

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

7.2.1. Selection and Timing of Doses

The SC dose of insulin (LY900014 and Humalog) will be individualized per patient to cover the carbohydrate content of the standardized liquid test meal based on the results from the dose-finding assessment (see Section 9.2.1). The individualized insulin dose of LY900014 and Humalog for each patient must be kept identical for the test meals throughout the crossover periods.

All study treatments will be given subcutaneously in the CRU by qualified and appropriately trained site personnel as designated by the investigator. During the dose-finding and study MMTT assessments, injections should be administered subcutaneously in the abdominal area, approximately 5 cm from the umbilicus. Injection technique details are provided to the site in separate, product-specific documentation. Injections will be rotated among different injection sites on the anterior abdominal wall during the 4 study periods (that is, left lower quadrant and right lower quadrant). Study injections should be given by a limited number of individuals for consistency.

Patients will be provided with the appropriate Humalog Kwikpens for self-administration during the outpatient period(s) of the study. Patients will be instructed to select and rotate their injection sites in the abdominal area and to administer the treatment subcutaneously.

The doses during the inpatient period will be administered immediately before or 20 minutes following the start of a test meal and will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the patient's case report form (CRF).

7.3. Blinding

This is a patient- and investigator-blind study. Blinding will be maintained throughout the conduct of the study as described in a separate blinding document. CCI used to administer either LY900014 or Humalog will be open-label and site will enact appropriate measures to ensure patient blinding. 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.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. 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 during the study MMTT procedure. However, dose adjustments may be made during the insulin transition period or washout periods based on the recommendation of site investigator.

7.4.1. Special Treatment Considerations

For daily dosing during the approximate 2-week lead-in/insulin transition period and between study periods until study completion, patients will be provided with Humalog U-100 CCI and commercially available insulin glargine for self-administration.

Commercially available insulin glulisine and 20% dextrose will be used during the run-in period to stabilize blood glucose prior to the start of the meal test. Insulin glulisine may also be used to treat hyperglycemia during the meal test (see Section 9.5.8).

7.5. Preparation/Handling/Storage/Accountability

LY900014 and the Humalog will be administered by CCI

During the inpatient stays, all study treatments will be given subcutaneously in the CRU by qualified and appropriately trained site personnel as designated by the investigator.

All clinical study material provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained. The investigator site will be permitted to destroy the investigational material after written approval is obtained from the sponsor and must retain appropriate documentation for the destruction of the material.

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

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Before use, store refrigerated (2°C - 8°C; 36°F - 46°F). Do not freeze. Once in use, store below 30°C (86 °F). Protect from direct heat and light. Once in use, do not refrigerate and use within 28 days.

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

7.6. Treatment Compliance

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

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

The specifications in this protocol for the timings of safety, PK, and GD sampling are given as targets, to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure to obtain samples due to clinical issues, such as problems with venous access, will not be considered a protocol violation, but written documentation will have to be provided to the sponsor for all missing samples (regardless of reasons) to facilitate data reconciliation before study completion.

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

7.7. Concomitant Therapy

Patients will continue the basal insulin regimen established during the insulin transition period throughout the entire study except when presenting safety issues (see Section 7.4); in this case, the investigator will discuss a change of the regimen of basal insulin to prevent any medical problems. Any change in the basal insulin regimen will be captured in the patient diary and CRF.

Patients may continue their stable concomitant medication at the time of study entry at regular, unchanged doses during the study (for example, antihypertensive medication, lipid-lowering agent, thyroid hormone replacement medication, hormonal contraception or hormonal replacement therapy).

Drugs that are known inducers, or inhibitors of cytochrome P450 (CYP) 2C8 are specifically excluded. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

In general, the addition of new concomitant medication should be avoided; however, paracetamol (maximum 4g/24hours) may be administered at the discretion of the investigator for treatment of headaches etc. If the need for concomitant medication (other than paracetamol) arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP. Any medication used during the course of the study must be documented.

Patients should not initiate new over-the-counter or prescription medication or nutritional supplements that affect blood glucose or the body's sensitivity to insulin or that promote weight loss 14 days before dosing or throughout the study.

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

7.8. Treatment after the End of the Study

Patients will continue their previous insulin regimen after the final study MMTT and associated procedures have been completed.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient meets 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%)
- ALP (alkaline phosphatase) >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 enrollment criteria and was inadvertently enrolled, the patient must be discontinued from the study.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - 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 hypo- or hyperglycaemic episode (see Section 9.5.6.3 and Section 9.5.6.2)
- Patient Decision
    - the patient 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.

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study

9.2. Visit Description

9.2.1. Lead-In and Insulin Transition

After completing all screening procedures according to the Schedule of Activities (Section 2), patients will return to the CRU for the lead-in visit and receive instructions on the insulin transition. The lead-in site visit is to take place at least 2 weeks prior to Period 1, Day -2. At the lead-in site visit, patients will switch from their prescribed short-acting insulin to Humalog provided by the site. Patients will also transition from their current regimen of basal insulin to site-provided insulin glargine according to the following guidance:

- At least 2 weeks prior to CRU admission for Period 1, Day -2, patients will switch from either NPH insulin, insulin detemir or insulin glargine to using site-provided insulin glargine. The starting dose will be at the investigator's discretion using patient's current insulin regimen as reference.
- Adjustments may be made in consultation with site investigator following feedback obtained from the patient during at least twice-weekly telephone follow-up as part of the insulin-transition period.
- Once a stable dose has been established, patients will remain on it through to study completion

Additionally, at the lead-in site visit, patients will be provided with general diabetes training including, but not limited to: proper insulin-injection technique, dose calculation for short-acting insulins, correct self-monitoring of plasma glucose with a standardized glucometer, and interpretation of results, symptoms, and treatment of hypoglycemia. In addition to the study

insulin, the site will also provide the glucose meter, test strips, control solution, and lancets. A diary will also be provided as described in section 9.5.7.

9.2.2. Dose-Finding Assessment

After transitioning to a stable dose of insulin glargine, patients may return to the CRU on Period 1, Day -1 in the early morning for the dose-finding assessment, which may begin between 07:00 and 11:00. Patients may arrive at the CRU on the evening of Day -2 if necessary. Patients will have fasted for at least 10 hours prior to the test meal (see Section 6.3.1). The objective of the dose-finding assessment is to determine an appropriate, individualized insulin lispro dose of LY900014 or Humalog to be administered with the standardized liquid test meal during the Study MMTT (see Section 9.2.3.2). The patient's blood glucose will be measured to select a Humalog dose for the dose-finding assessment meal test as follows:

- if the patient's blood glucose is within the range of 70 to 180 mg/dL (3.9 to 10.0 mM), the patient will be given Humalog at the dose the patient would have taken at home
- the dose-finding meal test should not be carried out if the patient's blood glucose is not within the range of 70 to 180 mg/dL (3.9 to 10.0 mM) prior to start of the dose-finding meal test. The dose-finding meal test may be rescheduled as judged by the investigator (see Section 6.2.1)

Immediately (within 1 minute) after the Humalog dose has been selected and administered, the patient will receive a standardized liquid test meal consisting of two cans of 8 fl/oz Abbott Ensure Plus (approximately 100 g of carbohydrates total in test meal). Patients are expected to complete each test meal within 15 minutes of starting the meal.

The patient's blood glucose will be measured every 20 minutes for 5 hours postmeal to select a Humalog dose for the MMTT as follows:

- if the patient's blood glucose is within the range of 70 to 240 mg/dL (3.9 to 13.3 mM), for 5 hours postmeal, the selected Humalog dose will be used for the insulin lispro dose (LY900014 and Humalog) to be administered with the MMTTs but can still be adjusted if necessary based on the clinical judgement of the investigator
- if the patient's blood glucose is not within the range of 70 to 240 mg/dL (3.9 to 13.3 mM), the dose of Humalog will be adjusted based on the investigator's judgement or if the investigator is unable to make a decision regarding the Humalog dose after completing the initial test, the dose-finding assessment may be repeated once within 3 days of the initial assessment
- if, during the dose-finding assessment, the patients' blood glucose drops below pre-test baseline, the site investigator may make further adjustments of the insulin lispro dose

Following completion of procedures associated with the dose finding assessment, patients may be offered a meal. Patients will remain inpatient at the CRU until the Study MMTT for Period 1 Day 1 the following day.

9.2.3. Study Period CRU Visits

9.2.3.1. Run-In

Before the start of the run-in period, the cannulation of 2 veins will be performed. A variable IV infusion of glucose (20% dextrose solution) or insulin glulisine will be initiated in order to obtain a blood glucose target level of 135 ±15 mg/dL (7.5 ±0.8 mmol/L). Any insulin infusion should be tapered off and stopped 30 minutes prior to start of the test meal. For the last 30 minutes prior to trial product administration, the target blood glucose concentration should be targeted without any glucose infusion. If this target glucose range is not attained before 11:00 AM, the meal test will be halted and may be performed on a separate visit; each meal test can only be repeated once (see Section 6.2.1 for rescheduling)

9.2.3.2. Study MMTT

Each patient's individual, short-acting insulin (Humalog) may be administered before the start of a standard dinner (at approximately 19:00). If a correction dose of short-acting insulin needs to be administered after the meal, no more than 6 U of short-acting insulin (Humalog) should be administered between 7 and 12 hours before the scheduled intake of liquid test meal

The meal test may start in the early morning at approximately 08:00 with allowance up to 11:00, if required, to ensure the patient's blood glucose is stable and at target, with the premeal activities as specified in the Schedule of Activities (Section 2). LY900014 and Humalog will be administered at two different times: either immediately before the start of the meal or 20 minutes following the start of the test meal at each of the 4 periods according to the randomisation sequence. For each MMTT, the patient should stay in a semisupine position for 2 hours postdose. The patient will not be allowed to consume water for 2 hours after the MMTT assessment begins; however, water may be consumed freely 2 hours postmeal.

A standardized liquid test meal will be administered on Day 1 for each of the 4 treatment periods. Patients are expected to complete each test meal within 15 minutes of starting the meal. Patients will be without further food intake from the start of the meal to completion of blood collection (approximately 420 minutes) unless required to treat hypoglycemia (see Section 9.5.8).

9.3. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational

product or the study, or that caused the patient to discontinue the investigational product before completing the study. The 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 categorise the severity of an AE as well as 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 investigational product, study device and/or study procedure and the AE.

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

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 CRF.

Hypoglycemic events are adverse events of special interest and will be collected and reported throughout the trial as described in Section 9.5.6.2. All hypoglycemic events will be recorded in the hypoglycemia module in the CRF this allows for the collection of comprehensive safety information relating to these events.

9.3.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
- when a condition related to the pre-filled pens necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

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

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

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

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

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

9.3.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.3.2. Complaint Handling

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

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

9.4. Treatment of Overdose

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

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia 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 intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

Refer to the Investigator's Brochure and/or Humalog Product Label.

9.5. Safety

9.5.1. Physical Examination

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

9.5.2. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2). Patients will be fasted for at least 8 hours prior to clinical laboratory tests taken at screening.

9.5.3. Vital Signs

For each patient, vital signs 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 at screening and semi-supine on Day 1.

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

If the patient feels unable to stand, semi-recumbent 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.

9.5.4. 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 investigational product, should be reported to Lilly, or its designee, as an AE via eCRF.

For each patient, a single12-lead digital electrocardiogram (ECG) will be collected according to the Schedule of Activities. 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/QTc interval from baseline) after enrollment, the investigator will determine if the patient can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an adverse event.

9.5.5. Other Tests

9.5.5.1. 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.

9.5.5.2. Body Weight and Height

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

9.5.6. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- adverse events

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

9.5.6.1. Hepatic Safety

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

9.5.6.2. Glucose Monitoring

Hypoglycemia will be described using the following definitions:

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

- **Severe hypoglycemia requiring medical attention**: a severe hypoglycemic event when patients require therapy by HCPs (EMTs, emergency room personnel, etc)

Other Hypoglycemia:

- **Nocturnal hypoglycemia:** any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking
- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, that do not require the assistance of another person, are accompanied by PG >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) hypoglycemia:** This optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category
- **Probable symptomatic hypoglycemia:** An event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

9.5.6.3. Severe Hypoglycemia

The determination of a hypoglycemic event as an episode of severe hypoglycemia 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.

All hypoglycemic events are adverse events of special interest and will be recorded in the hypoglycemia module of the CRF (see Section 9.3. for details). All episodes of severe hypoglycemia must be reported as SAEs.

9.5.6.4. 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 number, visit number, time after dosing, and a ruler for scaling.

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

9.5.7. Self-Monitored Plasma Glucose during Outpatient Period

Self-monitored plasma glucose (SMPG) testing will consist of a minimum of daily 4-point SMPG profiles (preprandial for 3 meals [that is, breakfast, lunch, and dinner] and at bedtime) using the glucometer provided by the site. Patients will be instructed to use a diary to document

any AEs, hypoglycemic events, insulin doses, and the SMPG values. During the lead-in/insulin transition and wash-out period, hyperglycemia will be monitored daily by fasting fingerstick glucose tests 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.

9.5.8. Treatment of Hyperglycemia and Hypoglycemia

Patients will be without food intake from the start of the MMTT to completion of blood collection (approximately 420 minutes) unless required to treat hypoglycemia, (see Section 9.5.6.2 for definition of hypoglycemia) with either rapidly absorbable oral carbohydrates or IV glucose.

Patients may consume up to 20 g of carbohydrates to treat or prevent hypoglycaemia during the fasting periods (See Sections 2, 6.3.1, and 9.2.2). If carbohydrates are administered and consumed, this must be captured in the patient's diary and eCRF.

If a patient is experiencing hyperglycemia (blood glucose concentration ≥ 306 mg/dL [17 mM]) for more than 1 hour, insulin glulisine will be administered intravenously.

In cases where treatment of either hypo- or hyperglycemia require intervention, samples for blood glucose will be taken and PK samples will be collected as planned.

9.6. Pharmacokinetics Samples

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.

9.6.1. Bioanalysis

Samples will be analyzed 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 investigational product concentrations will be retained for a maximum of 1 year following last patient visit for the study.

9.7. Pharmacodynamics

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.

9.7.1. Glucodynamics Samples

Blood samples (approximately 0.2 mL each) will be obtained for the measurement of glucose at the times specified in the Schedule of Activities (Section 2) using a validated method (for example, glucose analyzer) that will be readily available at the investigative site during the inpatient periods in order to provide real-time glucose measurement. Repeat samples for counter-checking of apparent spurious results may be taken where indicated. Samples will be disposed of upon confirmation of results.

9.7.1.1. Glucose Samples (Run-In Period)

Blood glucose concentrations will be monitored at a minimum of 30-minute intervals during the run-in period on Day 1 (from approximately 7 hours before dosing).

9.7.1.2. Glucose Samples (MMTT)

Blood samples will be obtained for the measurement of glucose at the times specified in the Schedule of Activities. These glucose measurements will be used for patient safety management as well as for GD evaluations.

9.7.2. Samples for Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro as described in the Section of Activities (Section 2). Additional samples may be collected if there is a possibility that an AE is immunologically mediated. Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies in the presence of insulin lispro. 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 Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the investigational product. 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 investigational product 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 utilized, data generated will be used only for the specific research scope described in this section.

9.9. Biomarkers

Not applicable for this study.

9.10. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

An initial 36 patients may be enrolled in order that approximately 30 patients complete the study. Thirty completing patients will provide greater than 95% power to demonstrate a 2-fold increase in the serum insulin lispro AUC(0-30min) between LY900014 and the Humalog. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The sample size will also provide greater than 95% power to demonstrate a 35% reduction of early 50% $t_{max.}$ The estimated standard deviation of within-subject difference on the log scale is 0.35 for AUC(0-30min) and 0.25 for early 50% tmax, according to an analysis of internal Lilly data (Study I8B-FW-ITRG [ITRG]) for LY900014 and Humalog administered in a repeat-dose study.

With this sample size, there is approximately 80% power to detect a -30 mg·h/dL difference (LY900014 versus Humalog when both are given immediately before meals) in postprandial glucose ΔAUC[0-2h]. This is based on an analysis of ITRG which showed a standard deviation of within-patient difference of 56.20 mg·h/dL on the original data scale.

Patients who are randomized but drop out before completing assigned treatment may be replaced to ensure that approximately 30 patients complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of patient disposition will be recorded and provided at the end of the study. All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

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

Primary statistical analyses of PK and GD parameters will be conducted on the set of patients who complete all treatment periods as the PK parameters and GD response is dependent on the insulin dose which is individualized by patient. Supportive analyses may be done on the key parameters for the patients who complete at least one period of treatment.

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.

Safety analyses will be conducted on the set of patients receiving at least 1 dose of the study drug to which they are randomized, regardless of whether or not they completed all protocol requirements.

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

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 treatment- and protocol procedure-related AEs will be listed, and if the frequency of events allows, safety data (including hypoglycemic events) will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator (see Section 6.3.1). Symptoms reported to occur prior to study entry/enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

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

10.3.1.2. Statistical Evaluation of Safety

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Patients who complete at least 1 MMTT and have measurable insulin lispro concentrations will be included in the analysis dataset for the PK analyses. PK analyses will be conducted using standard noncompartmental methods of analysis CCI [redacted]) on a computer that meets or exceeds the minimum system requirements for these programs. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

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}), $t_{1/2}$, AUC from time zero to time t, where t is the last time point with a measurable concentration [AUC(0-tlast)], AUC from time 0 to 30 minutes [AUC(0-30min)], AUC from time

zero to 1 hour [AUC(0-1h)], AUC from time zero to 7 hours [AUC(0-7h)], AUC from time 3 to 7 hours [AUC(3-7h)] 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.

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

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

10.3.2.2. Pharmacokinetic Statistical Inference

Patients who did not keep identical insulin lispro doses for the MMTTs across all periods will be excluded from the statistical analysis of the PK parameters.

Log-transformed AUCs, C_{max}, CL/F and Vz/F for insulin lispro will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog, and their corresponding 95% CIs of the ratios using the mixed-effects model that includes treatment (LY900014, Humalog) and period as fixed effects and patient as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters (early 50% tmax, late 50% tmax, tmax, and $t_{1/2}$). Least-squares means (LSmeans), treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between least squares (LS) means will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow and Liu 2009).

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

10.3.3. Glucodynamic Analyses

10.3.3.1. Glucodynamic Parameter Estimation

Patients who receive at least 1 dose of study drug and have evaluable GD data will be included in the analysis set for the GD analyses.

Data will be analyzed for the patients during each MMTT. The change from baseline values (the average of -30, -15, and 0 minutes represented as the 0-hour time point prior to the start of the MMTT) for each patient will be calculated. The area under the baseline subtracted glucose concentration versus time curve from time 0 to 2hr (ΔAUC[0-2h] and area under the baseline subtracted glucose concentration versus time curve from time 0 to 5hr post meal (ΔAUC[0-5h]) will be calculated. In addition, the change from baseline maximum glucose observed during the 5 hours postmeal and change from baseline 1 hour glucose and 2 hour glucose post the start of the meal will be calculated. Other partial ΔAUCs may be calculated, as deemed appropriate.

Parameters will be individually calculated for each patient and presented by summary statistics.

10.3.3.2. Glucodynamic Statistical Inference

Patients who did not complete the entire meal or had significant changes in nutrient consumption of the standardized liquid test meal or dose changes during the MMTTs will be excluded from all the statistical analysis of the GD parameters.

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented by treatment and by timing of dose (all 4 combinations of treatment and timing of dose). The GD parameters on the original scale (not log-transformed) will be analyzed using a statistical model that includes treatment, timing of dose (0 [immediately before the test meal], 20 minutes following the start of test meal), treatment-by-timing of dose interaction, and period as fixed effects and patient as a random effect. The p-value on the difference between LSmeans will be used to determine statistical significance and the corresponding 95% CIs for the LSmean ratios from Fieller's theorem will be presented.

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

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. Interim Analyses

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

11. References

AMIS database. 13 June 2006. DIMDI (Deutsches Institut für medizinische Dokumentation und Information. Available at: https://www.dimdi.de/dynamic/de/db/recherche/index.htm. Accessed: November 07, 2017.

Chow SC & Liu JP. Design and analysis of bioavailability and bioequivalence studies. 3rd ed. Florida: Taylor and Francis Group, LLC; 2009:88-90

Humalog [package insert]. Indianapolis, IN: Eli Lilly and Company; 2015.

CCI [package insert]. Research Triangle Park, NC: United Therapeutics Corp; 2014.

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received
BMI	body mass index
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist
CRF	case report form
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
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

GCP	good clinical practice
GD	glucodynamic
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
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 authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IMP	investigational medicinal product
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
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
MMTT	mixed meal tolerance test
Non-investigational product	A product that is not being tested or used as a reference in the clinical study, but is provided to patients and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
OAD	oral antidiabetics
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PAH	pulmonary arterial hypertension
randomize	the process of assigning patients to an experimental group on a random basis
PD	pharmacodynamic
PK	pharmacokinetic
SAE	serious adverse event

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.
SMBG	self-monitored blood glucose
SMPG	self-monitored plasma glucose
SPC	Summary of Product Characteristics
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets

Absolute counts of:
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Leucocytes
- Microscopy[d]

Clinical Chemistry[a]
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphorus
- HbA1C[b]
- Glucose fasting
- C-peptide[b]
- Blood urea nitrogen (BUN)
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine
- Gamma-glutamyl transferase (GGT)

Breath ethanol testing[c]
Urine drug screen[b,c]
Hepatitis B surface antigen[b]
Hepatitis C antibody[b]
HIV[b]
Pregnancy test [e]
FSH [b]

International normalised ratio (INR)[b]
Partial thromboplastin time (PTT)[b]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

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

b Performed at screening only

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

d If clinically indicated, per investigator's discretion

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

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Recruitment

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

Ethical Review

The investigator or appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by 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 or Patient Information Leaflet, Package Insertor Summary of Product Characteristics and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

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

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the 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 or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

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

Appendix 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 Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated 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 normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I8B-MC-ITRV Sampling Summary

Purpose	Blood Volume per Sample(s) (mL)	Number of Blood Samples	Total Volume (mL)
Screening	11	1	11
Clinical laboratory tests[a]	9	2	18
Dose finding assessment	0.2	15	3
Blood glucose sampling (run-in)	0.2	14 samples x 4 periods = 56	11.2
Blood glucose sampling (MMTT)	0.2	24 samples x 4 periods = 96	19.2
Pharmocokinetics – insulin lispro	2.5	22 samples x 4 periods = 88	220
Immunogenicity	5	4	20
Pharmacogenetics	10	1	10
Total			312.4
Total for clinical purposes			320

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

Appendix 6. Protocol Amendment I8B-MC-ITRV(b) Summary: A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog® in Patients with T1DM

Overview

Protocol I8B-MC-ITRV A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 compared to Humalog® in Patients with T1DM has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

Changes to the protocol made to clarify text and correct mis-statements are listed below:

- Correction in Appendix 6 of protocol amendment (a) to the inclusion criterion that all patients included in the study have a diagnosis of T1DM which is consistent with the inclusion criterion in Section 6.1
- Clarification that Remodulin® was initially given approval in Germany in 2006
- Clarification of Schedule of Activities in line with Appendix 2 that serum pregnancy test will be performed for all females
- Clarification of fasting status in Schedule of Activities and Section 6.3.1 in line with fasting blood glucose required at follow-up as presented in Appendix 2
- Clarify that vital signs will be taken supine at screening and semi-supine on Day 1
- Establish consistency of dose-finding assessment from 07:00 to 11:00 throughout the protocol
- Clarify patients are to remain inpatient at the CRU following completion of the dose-finding assessment conducted on Day -1 until completion of Day 1 procedures
- Clarify that patients may consume up to 20 g of carbohydrates to treat or prevent hypoglycemia (regardless of hypoglycemia level) during fasting periods.

Revised Protocol Sections

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

Study Schedule Protocol I8B-MC-ITRV

	Sign Informed Consent	Screening	Lead-in	Study Period (Periods 1 to 4)		Follow-up/Early discontinuation	Comments
Procedure		Days -30 to -17	14 days prior to Day -2	Day -1	Day 1	≥ 14 days after discharge	
….							
Vital signs~~(semi-recumbent)~~: blood pressure and pulse rate		X			Predose, 30 and 120 minutes postdose	X	Vital signs will be taken while patients are supine at screening and semi-supine on Day 1.
12-lead ECG		X			Predose (Period 1)	X	Single ECGs will be collected for safety.
Clinical laboratory tests		X			Predose for Period 1 only	X	Fasting laboratory test for screening and follow-up. Screening laboratory tests will be analyzed at a local laboratory (see Section 9.5.2). ~~Follow-up screening not fasted.~~
…..							
Pregnancy test		X		X		X	~~For female patients of childbearing potential only.~~ Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at admission for Period 1 and at follow-up (see Appendix 2)

3.2 Background

…

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 (Remodulin®) 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 (Tyvaso®), 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 2006~~2007~~ (AMIS database [WWW])~~Remodulin package insert, 2014~~).

6.3.1 Meals and Dietary Restrictions

Patients will be fasted (except for water) for at least 10 hours before each test meal and 8 hours prior to screening and follow-up assessments (see Section 9.5.8 for guidelines on hypoglycemia treatment). The patient will not be allowed to consume water for 2 hours after the MMTT assessment begins; however, water may be consumed freely 2 hours postmeal.

9.2.2 Dose-Finding Assessment

After transitioning to a stable dose of insulin glargine, patients may return to the CRU on Period 1, Day -1 in the early morning for the dose-finding assessment, which may begin between 07:00 and ~~09~~11:00.

…

Following completion of procedures associated with the dose finding assessment, patients may be offered a meal. Patients will ~~have the option to~~ remain inpatient at the CRU until the Study MMTT for Period 1 Day 1 the following day.

9.5.3 Vital Signs

For each patient, vital signs 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 at screening and semi-~~recumbent~~ supine on Day 1.

9.5.8 Treatment of Hyperglycemia and Hypoglycemia

Patients will be without food intake from the start of the MMTT to completion of blood collection (approximately 420 minutes) unless required to treat hypoglycemia (see Section 9.5.6.2 for definition of hypoglycemia) with either rapidly absorbable oral carbohydrates or IV glucose.

Patients may consume up to 20 g of carbohydrates to treat or prevent hypoglycemia ~~(Level 2 ≤ 54 mg/dL [see Section 9.5.6.2]~~ during the fasting periods (See Sections 2, 6.3.1, and

9.2.2). If carbohydrates are administered and consumed, this must be captured in the patient's diary and eCRF.

11 References

AMIS database. 13 June 2006. DIMDI (Deutsches Institut für medizinische Dokumentation und Information. Available at: https://www.dimdi.de/dynamic/de/db/recherche/index.htm. Accessed: November 07, 2017.

Chow SC & Liu JP. Design and analysis of bioavailability and bioequivalence studies. 3rd ed. Florida: Taylor and Francis Group, LLC; 2009:88-90

Humalog [package insert]. Indianapolis, IN: Eli Lilly and Company; 2015.

Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corp; 2014.

Appendix 6. Revised Protocol Sections

6.1. Inclusion Criteria

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

[1] are male or female patients with T1~~2~~DM for at least 1 year. A diagnosis of T1~~2~~DM is based on medical history with a fasting C-peptide <0.30 nmol/L.