Protocol: I8B-MC-ITSA(d)

A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Compared to Humalog in Children, Adolescents, and Adults With Type 1 Diabetes Mellitus

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A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Compared to Humalog in Children, Adolescents, and Adults with Type 1 Diabetes Mellitus

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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 children, adolescents, and adults with type 1 diabetes mellitus

Rationale:

A prandial insulin with faster-on and/or faster-off characteristics might reduce glycaemic excursions and the incidence of postprandial hypoglycaemia compared to currently available fast-acting insulin analogues. LY900014 is an ultra-rapid-acting insulin lispro formulation with increased early absorption compared to commercially available insulin lispro formulation (Humalog®; Eli Lilly and Company). LY900014 aims to mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions.

The aim of the study is to evaluate insulin lispro pharmacokinetics (PK), glucodynamics (GD), safety, and tolerability of LY900014 in comparison with Humalog following a single subcutaneous (SC) dose administration immediately prior to a standardised liquid meal in paediatric and adult patients with type 1 diabetes mellitus (T1DM). This will be the first study to evaluate LY900014 in paediatric patients with T1DM.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
1. Part A: To evaluate the PK of insulin lispro following a single SC dose administered through injection of LY900014 compared to Humalog in children, adolescents, and adults with T1DM	1. Early 50% t_{max} and AUC(0-30min)
2. Part B: To evaluate the PK of insulin lispro following a single SC bolus dose administered through CSII of LY900014 compared to Humalog in children, adolescents, and adults with T1DM	2. Early 50% t_{max} and AUC(0-30min)
Secondary	
1. Part A and Part B: To evaluate the difference in GD response to LY900014 and Humalog administered through SC bolus injection or CSII, as assessed using the liquid MMTT in children, adolescents, and adults with T1DM	1. ΔAUC(0-2h), ΔAUC(0-5h)
2. Part A and Part B: To evaluate the tolerability of LY900014 following SC injection or CSII in children, adolescents, and adults with T1DM	2. AEs including injection/catheter insertion site reactions/pain, hypoglycaemia, and anti-insulin lispro antibodies

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; AUC(0-30min) = AUC from time zero to 30 minutes; CSII = continuous subcutaneous insulin infusion; ΔAUC = area under the baseline subtracted glucose concentration versus time curve; ΔAUC(0-2h) = ΔAUC from time 0 to 2 hours postmeal; ΔAUC(0-5h) = ΔAUC from time 0 to 5 hours postmeal; early 50% t_{max} = 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-ITSA is a randomised, patient- and investigator-blind, 2-part study, with each part containing a 2-period crossover assessment in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years) with T1DM to evaluate the PK, GD, and tolerability of LY900014 compared to Humalog given as a bolus either as a SC injection or via a continuous subcutaneous insulin infusion (CSII) pump.

Treatment Arms and Planned Duration for an Individual Patient:
The study will be conducted in 2 parts, Part A and Part B. Each part consists of a 2-period crossover to compare LY900014 and Humalog administered prior to a mixed meal tolerance test (MMTT). All study and treatment procedures will be conducted during inpatient stays of approximately 2 days per period and require a minimum of 3 days and a maximum of 23 days to complete both periods. In each part, after completion of the last study period (Period 2), a 14-day safety follow-up is planned. Total duration of each part is expected to be up to 68 days. Patients are encouraged to participate in both Part A and Part B of the study; however, study participation is not contingent on patients' participation in both parts of the study.

Patients may be screened up to 28 days prior to Day -1 of Period 1 of Part A and Part B. Patients will be admitted to the study site the day before the MMTT day each period and will remain until all assessments are completed on Day 1. On Day 1 in Period 1 for Part A and on Day -1 in Period 1 for Part B, patients will be randomised to 1 of 2 treatment sequences. In Part A, each patient will receive a single SC injection of both LY900014 and Humalog immediately prior to an MMTT assessment in a crossover design. Initiation of Part B of the study may begin pending the review of the PK, GD, safety, and tolerability data from Part A and ongoing or planned adult CSII Phase 1b studies. In Part B, patients will receive a single SC bolus dose of both LY900014 and Humalog via CSII pump immediately prior to an MMTT assessment in a crossover design. Patients will undergo a follow-up visit at least 14 days after the last dose of the study drug in each part.

Treatment:

Part A: Each patient will receive a single SC bolus injection of LY900014 and Humalog.

Part B: Each patient will receive a single SC bolus of LY900014 and Humalog via CSII pump.

Number of Patients:
Approximately 45 patients may be enrolled into the study so that approximately 36 patients (12 patients in each age group [6 to <12 years, 12 to <18 years, and 18 to <65 years] based on the age at initial screening) complete both inpatient periods in both parts of the study.

Patients participating in Part A may continue participation in Part B. If patients from Part A decline participation in Part B or drop out from Part A, additional patients will be enrolled to ensure approximately 36 patients (12 patients in each age group) complete both periods in Part B of the study.

Statistical Analysis:
The analyses for Part A and Part B will be conducted separately using similar statistical methods. Primary statistical analyses will be conducted on the set of patients who complete both treatment periods. Supportive analyses may be done on the key parameters for the patients who complete at least 1 treatment period. Safety analyses will be conducted for the set of patients receiving at least 1 dose of the study drug, whether or not they completed all protocol requirements.

Safety: All study drug- and protocol procedure-related adverse events will be listed, and if the frequency of events allows, safety data (including hypoglycaemic events) will be summarised using descriptive methodology. Safety parameters will be listed, and may be summarised using standard descriptive statistics.

Pharmacokinetic: Log-transformed PK parameters for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog, and their corresponding 95% CIs of the ratios using the mixed-effect model that includes treatment, sequence, period, age group, and treatment by age group interaction as fixed effects and patient within sequence as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters (time to early half-maximal drug concentration [early 50% t_{max}], time to late half-maximal drug concentration [late 50% t_{max}], time of maximum observed drug concentration (t_{max}). Least-squares means (LSmeans), treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios using the Fieller's theorem will be provided.

Glucodynamic: Data will be analysed 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 (ΔAUC) from time 0 to 2 hours postmeal (ΔAUC[0-2h]) and ΔAUC from time 0 to 5 hours postmeal (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 after the start of the meal will be calculated. Other partial ΔAUCs may be calculated as deemed appropriate.

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented by treatment for each age group. The GD parameters on the original scale (not log transformed) will be analysed using the same model used for PK parameters. Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using the Fieller's theorem.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITSA (Part A)

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	101	Telephone Visit	1 and 2		801	
Day	Within 28 days Prior to Day -1	≥Day -10[c]	-1[d]	1	≥14 days After Last Dose of Study Drug	
Informed Consent/Assent	X					Should be obtained before any study-related procedures are performed.
Inclusion/Exclusion Criteria	X					
Medical History	X					
Pre-existing Conditions	X					
Age	X					
Height	X					
Weight	X			X	X	
Physical Examination	X			Predose	X	Physical examination at screening. Thereafter, targeted medical assessment, as appropriate.
Admission to Study Site			X			
IWRS and Randomisation				X		Randomisation in Period 1 only. Age group for randomisation will be based on initial screening.
Previous Diabetes Therapy Record Prandial and Basal Insulin Dose	X			X*		*Period 1 only.
Vital Signs (Pulse, Sitting BP)	X			Pre- and 2 hours postdose	X	
Eligibility Assessment	X	X	X*			*Period 1 only.
Hip and Waist Circumference			X			Applicable only to adult patients.

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	101	Telephone Visit	1 and 2		801	
Day	Within 28 days Prior to Day -1	≥Day -10[c]	-1[d]	1	≥14 days After Last Dose of Study Drug	
Clinical Laboratory Tests	X				X	See Appendix 2 for details. All patients of legal drinking age (according to local laws) will receive alcohol breath test on Day -1.
Glycated Haemoglobin (HbA1c) Assessment	X					
Urinalysis	X				X	
12-Lead ECG	X					
Pregnancy Test	X		X		X	Pregnancy tests will be performed for all females ≥12 years of age or <12 years of age with onset of menses. Serum pregnancy tests will be performed at screening, and urine pregnancy test on Day -1 of Periods 1 and 2 (or when clinically indicated), and at the follow-up or ED visit. Urine pregnancy tests at other visits accepted per local regulations.
Provide Evening Meal			X			
Begin Overnight Fast			X			Patients will be fasted (except for water) for at least 10 hours before each test meal.
Stop CSII			X			Prior to start of run-in. Applicable only to patients on

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	101	Telephone Visit	1 and 2		801	
Day	Within 28 days Prior to Day -1	≥Day -10[c]	-1[d]	1	≥14 days After Last Dose of Study Drug	
						CSII.
Run-in/Stabilisation of Glucose			X (following evening meal)			Approximately at 09:00 to 10:00 PM infusion of glucose (dextrose solution) or CCI insulin to target a blood glucose concentration of 135±25 mg/dL (7.5±1.4 mmol/L). Blood glucose concentrations will be monitored at a minimum of 30- to 60-minute intervals.
Study Drug Administration (Single SC injection)				X		Time of study drug administration = 0 hour. Study drug will be administered at approximately the same times on Day 1 of each study period.
Immunogenicity Sample				Predose	X	
Injection-Site Evaluation				0, 60, and 240 minutes postdose		Time 0: Assessments of injection-site local tolerability will occur immediately following the injection.
Directions for Preparing for PK and MMTT Visits		X				Patients will receive preparatory instructions as part of their pre-study telephone consultation (see Section 6.3, for details).
Mixed Meal Tolerance Test (MMTT)				X		A standard liquid meal will be administered at the MMTT time "0" (as soon as possible after

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	101	Telephone Visit	1 and 2		801	
Day	Within 28 days Prior to Day -1	≥Day -10[c]	-1[d]	1	≥14 days After Last Dose of Study Drug	
						administration of study drug) and should be consumed within 15 minutes.
Blood Glucose Sampling (MMTT)				-30, -15, 0 (premeal), 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300 minutes postmeal		Time is referenced to meal start time, i.e., time 0. Time 0 is collected immediately prior to start of meal consumption.
Insulin Lispro PK Sampling				0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 90, 120, 150, 180, 240, 300, 360, and 420 minutes postdose		Sampling times are relative to the time of study drug treatment administration (t = 0) in each period
Transition to NPH Twice Daily Therapy 7-3 days Prior to Day -1		X				Applicable only to patients using multiple daily injection therapy. Patient can return to pre-study basal insulin following completion of MMTT sampling period per investigator's decision and allowing for transition to NPH prior to next dosing.
Resume Prestudy CSII Rate				X		Applicable only to patients on CSII. CSII with the patient's prestudy insulin will be restarted after

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	101	Telephone Visit	1 and 2		801	
Day	Within 28 days Prior to Day -1	≥Day -10[c]	-1[d]	1	≥14 days After Last Dose of Study Drug	
						completion of assessment period (approximately 420 minutes postdose).
Adverse Events/Hypoglycaemia	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	
Patient Discharge from Study Site				X		If the next MMTT (Period 2) is scheduled on the next day, the patient may be discharged after the second MMTT (Period 2).

Abbreviations: BP = blood pressure; CSII = continuous subcutaneous insulin infusion; ECG = electrocardiogram; ED = early discontinuation; IWRS = Interactive Web Response System; MMTT = mixed meal tolerance test; NPH = neutral protamine Hagedorn; PK = pharmacokinetics; SC = subcutaneous.

a Safety follow-up visit should occur at least 14 days after the last dose.

b Early discontinuation procedures will be performed at least 14 days after a patient stops the study after receiving study drug on Day 1 of Period 1 and before Day 1 of Period 2.

c This is a telephone visit.

d In case of dosing on consecutive days, the medical assessments to be conducted on Day -1 of Period 2 may be done on Day 1 of Period 1.

Note: The study 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: pharmacokinetic samples including blood sampling for blood glucose and laboratory samples per protocol nominal times. Electrocardiograms 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.

Study Schedule Protocol I8B-MC-ITSA (Part B)

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	102	Telephone Visit	3 and 4		802	
Day	Within 28 days Prior to Day -1	≥ Day -10[c]	-1[d]	1	≥14 days After Discharge	
Informed Consent/Assent	X[e]					Should be obtained before any study-related procedures are performed.
Inclusion/Exclusion Criteria	X					
Medical History	X					
Pre-existing Conditions	X					For patients continuing from Part A, a review will be performed to record any changes from the previous screening.
Age	X					Applicable only to newly enrolled patients. For patients participating from Part A, age at initial screening (Part A) will be used for reporting purposes.
Height	X					
Weight	X		X		X	
Physical Examination	X			Predose	X	Physical examination at screening. Thereafter, targeted medical assessment, as appropriate.
Admission to Study Site			X			

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	102	Telephone Visit	3 and 4		802	
Day	Within 28 days Prior to Day -1	≥ Day -10[c]	-1[d]	1	≥14 days After Discharge	
IWRS and Randomisation			X			Randomisation at Period 1 only. Age group for randomisation will be based on initial screening.
Previous Diabetes Therapy Record Prandial and Basal Insulin Dose	X			X*		*Period 1 only.
Vital Signs (Pulse, Sitting BP)	X			Pre- and 2 hours postdose	X	
Hip and Waist Circumference			X			Applicable only to adult patients.
Eligibility Assessment	X	X	X*			*Period 1 only.
Clinical Laboratory Tests	X				X	See Appendix 2 for details. All patients of legal drinking age (according to local laws) will receive alcohol breath test on Day -1.
Glycated Haemoglobin (HbA1c) Assessment	X					
Urinalysis	X				X	
12-Lead ECG	X					

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	102	Telephone Visit	3 and 4		802	
Day	Within 28 days Prior to Day -1	≥ Day -10[c]	-1[d]	1	≥14 days After Discharge	
Pregnancy Test	X		X		X	Pregnancy tests will be performed for all females ≥12 years of age or < 12 years of age with onset of menses. Serum pregnancy tests will be performed at screening, and urine pregnancy test on Day -1 of Periods 1 and 2 (or when clinically indicated), and at the follow-up or ED visit. Urine pregnancy tests at other visits accepted per local regulations.
Provide Evening Meal and Administer Bolus Insulin Infusion			X			Provide instructions for replacement of pump reservoir/tubing/infusion set containing IP to occur following evening meal. Prandial insulin to be patient's usual insulin.
Begin Overnight Fast			X			Patients will be fasted (except for water) for at least 10 hours before each test meal.

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	102	Telephone Visit	3 and 4		802	
Day	Within 28 days Prior to Day -1	≥ Day -10[c]	-1[d]	1	≥14 days After Discharge	
Reduce CSII basal rate			X			Prior to start of run-in. Applicable only to patients on CSII. Basal rate to be reduced to 0.1 U/hour.
Run-in/Stabilisation of Glucose			X (following evening meal)			Approximately at 09:00 to 10:00 PM infusion of glucose (dextrose solution) or CCI [redacted] insulin to target a blood glucose concentration of 135±25 mg/dL (7.5±1.4 mmol/L). Blood glucose concentrations will be monitored at a minimum of 30- to 60-minute intervals.
Study Drug Administration (Single Bolus via CSII)				X		Time of study drug administration = 0 hour. Study drug will be administered at approximately the same times on Day 1 of each study period.
Immunogenicity Sample				Predose	X	

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	102	Telephone Visit	3 and 4		802	
Day	Within 28 days Prior to Day -1	≥ Day -10[c]	-1[d]	1	≥14 days After Discharge	
Catheter-Site Evaluation				0, 20, 40, 60, and 240 minutes postdose		Time 0: Assessments will occur immediately following the study drug administration.
Directions for Preparing for PK and MMTT Visits		X				Patients will receive preparatory instructions as part of their pre-study telephone consultation (see Section 6.3, for details).
Mixed Meal Tolerance Test				X		A standard liquid meal will be administered at the MMTT time "0" (as soon as possible after administration of study drug) and should be consumed within 15 minutes.
Blood Glucose Sampling (MMTT)				-30, -15, 0 (premeal), 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300 minutes (postmeal)		Time is referenced to meal start time. Time 0 is collected immediately prior to start of meal consumption.

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	102	Telephone Visit	3 and 4		802	
Day	Within 28 days Prior to Day -1	≥ Day -10[c]	-1[d]	1	≥14 days After Discharge	
Insulin Lispro PK Sampling				0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 90, 120, 150, 180, 240, 300, 360, and 420 minutes postdose		Sampling times are relative to the time of study drug treatment administration (t = 0) in each period.
Transition to NPH Twice Daily Therapy 7-3 days Prior to Day -1		X				Applicable only to patients using multiple daily injection therapy. Patient can return to pre-study basal insulin following completion of MMTT sampling period per investigator's decision and allowing for transition to NPH prior to next dosing.
Resume Prestudy CSII Rate				X		Applicable only to patients on CSII. CSII with the patient's prestudy insulin will be restarted after completion of assessment period (approximately 420 minutes postdose).
Adverse Events/Hypoglycaemia	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	

Visits	Screening		Study Periods (Periods 1 and 2)		Follow-up[a]/Early Discontinuation[b]	Comments
	102	Telephone Visit	3 and 4		802	
Day	Within 28 days Prior to Day -1	≥ Day -10[c]	-1[d]	1	≥14 days After Discharge	
Patient Discharge from Study Site				X		If the next MMTT (Period 2) is scheduled on the next day, the patient may be discharged after the second MMTT (Period 2).

Abbreviations: BP = blood pressure; CSII = continuous subcutaneous insulin infusion; ECG = electrocardiogram; ED = early discontinuation; IWRS = Interactive Web Response System; MMTT = mixed meal tolerance test; NPH = neutral protamine Hagedorn; PK = pharmacokinetics; SC = subcutaneous.

a Safety follow-up visit should occur at least 14 days after the completion of Period 2.

b Early discontinuation procedures will be performed at least 14 days after a patient stops the study after receiving study drug on Day 1 of Period 1 and before Day 1 of Period 2.

c This is a telephonic visit.

d In case of dosing on consecutive days, the medical assessments to be conducted on Day -1 of Period 2 may be done on Day 1 of Period 1.

e Not applicable for patients continuing from Part A.

Note: The study 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: pharmacokinetic samples including blood sampling for blood glucose and laboratory samples per protocol nominal times. Vital sign and measurements should be scheduled before but as close as possible to the PK sampling times. Catheter-site assessments can be performed after PK sampling.

3. Introduction

3.1. Study Rationale

A prandial insulin with faster-on and/or faster-off characteristics might reduce glycaemic excursions and the incidence of postprandial hypoglycaemia compared to currently available fast-acting insulin analogues. LY900014 is an ultra-rapid-acting insulin lispro formulation with increased early absorption compared to commercially available insulin lispro formulation (Humalog®; Eli Lilly and Company). LY900014 aims to mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions. This faster profile may help to overcome commonly observed difficulties in insulin therapy in paediatric patients such as increasing weight, height, and caloric needs as well as unpredictable eating behaviour of young children and peripheral resistance of puberty.

The aim of the study is to evaluate insulin lispro pharmacokinetics (PK), glucodynamics (GD), safety, and tolerability of LY900014 in comparison with Humalog following a single subcutaneous (SC) dose administration immediately prior to a standardised liquid meal in paediatric and adult patients with type 1 diabetes mellitus (T1DM). This will be the first study to evaluate LY900014 in paediatric patients with T1DM.

3.2. Background

The insulin analogue, insulin lispro (Humalog), has shown to be absorbed more quickly than regular human insulin (RHI) (Humalog package insert, 2015). In healthy volunteers given 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). The persistent delays in absorption and variability in the duration of action of currently available rapid-acting insulin analogues contribute to commonly observed difficulties of insulin therapy in youths (due to increasing weight, height, peripheral resistance of puberty, changes in caloric needs, and unpredictable eating behaviour of younger youths; Cengiz 2012). An ultra-rapid-acting prandial insulin would shift the PK/GD of insulin analogues so that they have an even faster onset to better match carbohydrate absorption and lead to improved postprandial glucose that also allows greater flexibility in the time of dosing relative to meals.

Regional evidence suggests that the incidence of T1DM in youths is increasing in the US (Lipman et al. 2013) and Europe (EURODIAB ACE Study Group 2000). Estimates of T1DM prevalence in the paediatric population in the US come from the Centers for Disease Control and Prevention-sponsored SEARCH for Diabetes in Youth (SEARCH) Study (SEARCH for Diabetes in Youth Study Group 2009), which collects diabetes diagnosis information from multiple centres throughout the US. This study estimated the 2001 prevalence of T1DM among children under 10 years of age to be 0.76 per 1000; amongst adolescents 10 to 19 years of age, the risk more than doubled to 2.28 cases per 1000. More recently, the SEARCH study estimated that in 2011 the total number of youth in the US <20 years of age with T1DM was 166,984 (Pettit et al. 2014). As with adults, intensive diabetes management through maintenance of tight glycaemic control helps to delay onset and slow the progression of complications of the disease in youths (DCCT 1993). Tight glycaemic control is achieved via intensive insulin therapy, which requires

dietary discipline, frequent blood glucose monitoring, and multiple injections of insulin (both rapid- and long-acting insulin) to mimic the natural pattern of insulin release, the combination of which represents a major burden on the patient, especially youths. Intensive insulin treatment in T1DM should be initiated early in disease progression and the improved glycaemic control may have a lasting impact on reducing the onset of diabetic complications.

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] as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient to elicit a sy[redacted]fect. Treprostinil is a prostacyclin analogue, administered either through inhalation [redacted], as an intravenous (IV) infusion, or as a continuous SC administration for the treatment of symptomatic pulmonary arterial hypertension (PAH) and has been approved in the US since 2002 and for SC administration in Germany since 2005 [redacted] In adults dosed with LY900014, systemic treprostinil was unmeasurable and no haemodynamic effects were noted with a treprostinil dose equivalent that contained in [redacted] of LY900014. Sodium citrate, an excipient that speeds up 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, concentration of the excipients 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 adult patients with diabetes (60 T1DM and 29 type 2 diabetes mellitus [T2DM]). The total insulin lispro exposure was similar between LY900014 and Humalog; however, LY900014 demonstrated a faster and earlier insulin lispro absorption compared to Humalog. LY900014 displayed proportional increases in insulin lispro exposure (area under the concentration versus time curve [AUC] and maximum observed drug concentration (C_{max}) with dose. The faster early insulin lispro absorption was maintained across the dose range studied (7.5 to 15 U). 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. Data from these Phase 1b studies show there was only 1 sample with quantifiable plasma treprostinil concentrations from approximately 472 samples taken from a total of 60 patients with T1DM and T2DM following administration of LY900014 using doses up to 50 U per SC bolus injection. In addition, no quantifiable plasma treprostinil concentrations were observed with continuous subcutaneous insulin infusion (CSII) therapy during the basal infusion or after the bolus dose in 30 patients. 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 hypoglycaemia. Additionally, there were 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 adult studies in healthy subjects 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 hypoglycaemia, hypersensitivity reactions (localised allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral oedema (Humalog package insert, 2015).

Notably, across all doses in the adult studies that have evaluated treprostinil as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those AEs associated with systemic absorption of treprostinil, as described in the CCI The exposures of treprostinil in LY900014 in this study are 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.

There are limited data on the use of treprostinil in paediatric patients. Paediatric assessments have not been required for treprostinil because of its orphan drug designation; thus, the safety and effectiveness of treprostinil in paediatric patients have not been established CCI . Subcutaneous treprostinil has been evaluated in children with PAH in an observational study (n=8). Patients initially received a fixed treprostinil dose of 1.25 ng/kg/min, which was gradually increased according to general and local tolerance, reaching a median of 40 ng/kg/min (range, 37 to 60 ng/kg/min) over the duration of follow-up (6- to 18-month time period) after initiation of treprostinil therapy. Six children had symptomatic and haemodynamic response to the addition of SC treprostinil, with manageable control of local injection-site discomfort (Levy et al. 2011). The amount of treprostinil will vary based upon the LY900014 dose administered CCI and treprostinil exposure has not been detected in adults a 1b multiple daily injection (MDI) studies or with CSII therapy during the basal infusion (up to 1.6 U/h containing 16 ng/h of treprostinil) or after the bolus dose CCI On average, the paediatric population will use a lower prepranaial insulin dose, further lowering exposure to treprostinil in this population.

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. Repeat SC dosing with treprostinil sodium for up to 26 weeks was well tolerated in rats and dogs. Survival was not affected in rats at doses up to 0.1 mg/kg/day and in dogs at doses up to 0.07 mg/kg/day. Clinical signs were limited to transient, dose-related flushing of the extremities secondary to the vasodilatory pharmacology of treprostinil in rats only. No evidence of injection-site reactions to treprostinil occurred either

when treprostinil was injected alone in 13- or 26-week repeat-dose toxicity studies in rats and dogs or when treprostinil was injected in combination with insulin lispro in a 2-week local tolerance study in rats. Furthermore, there was no indication of systemic target organ toxicity in either rats or dogs. No evidence of genotoxicity was demonstrated with treprostinil in a standard battery of genetic toxicity tests. There was no evidence of reproductive toxicity or teratogenicity in rats and no evidence of teratogenicity in rabbits [redacted] hus, there are no known potential risks associated with the use of small amounts of treprostinil [redacted] in the LY900014 formulation.

Additionally, local and systemic toxicity profiles of Humalog and [redacted] 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 further oral food intake following consumption of liquid test meal to completion of blood glucose collection (approximately 300 minutes) unless required to treat hypoglycaemia, as defined by the plasma glucose (PG) level ≤70 mg/dL (3.9 mM) with symptoms or any PG ≤60 mg/dL (3.0 mM) during the inpatient period, i.e., reversed with either rapidly absorbable oral carbohydrates or IV glucose. If a patient's blood glucose concentration rises above 300 mg/dL (16.7 mM) for more than 1 hour, RHI will be administered IV. Appropriate measures will be taken to minimise the risk of hyperglycaemia (see Section 9.4.6).

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

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

4. Objectives and Endpoints

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

Table ITSA.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
1. Part A: To evaluate the PK of insulin lispro following a single SC bolus dose administered through injection of LY900014 compared to Humalog in children, adolescents, and adults with T1DM	1. Early 50% t_{max} and AUC(0-30min)
2. Part B: To evaluate the PK of insulin lispro following a single SC bolus dose administered through CSII of LY900014 compared to Humalog in children, adolescents, and adults with T1DM	2. Early 50% t_{max} and AUC(0-30min)
Secondary	
1. Part A and Part B: To evaluate the difference in GD response to LY900014 and Humalog administered through SC bolus injection or CSII, as assessed using the liquid MMTT in children, adolescents, and adults with T1DM	1. ΔAUC(0-2h), ΔAUC(0-5h)
2. Part A and Part B: To evaluate the tolerability of LY900014 following SC injection or CSII in children, adolescents, and adults with T1DM	2. AEs including injection/catheter insertion site reactions/pain, hypoglycaemia, and anti-insulin lispro antibodies

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; AUC(0-30min) = AUC from time zero to 30 minutes; ΔAUC = area under the baseline subtracted glucose concentration versus time curve; ΔAUC(0-2h) = area under the baseline subtracted glucose concentration versus from time 0 to 2 hours postmeal; ΔAUC(0-5h) = area under the baseline subtracted glucose concentration versus from time 0 to 5 hours postmeal; CSII = continuous subcutaneous insulin infusion; early 50% t_{max} = time to early half-maximal drug concentration; GD = glucodynamics; MMTT = mixed meal tolerance test; PK = pharmacokinetic(s); SC = subcutaneous; T1DM = type 1 diabetes mellitus.

5. Study Design

5.1. Overall Design

This is a Phase 1, randomised, 2-part, patient- and investigator-blind, 2-period crossover study in children (age 6 to <12 years), adolescents (age 12 to <18 years), and adults (age 18 to <65 years) with T1DM currently using a CSII pump or MDIs. The aim is to evaluate insulin lispro PK, GD, and tolerability of LY900014 in comparison with insulin lispro (reference) following a single dose SC administration immediately prior to a standardised liquid meal.

During the screening visit, patients will receive a diary to document any AEs and/or hypoglycaemic events. Transition instructions pertinent to those patients receiving MDI who will transition their basal insulin to twice daily neutral protamine Hagedorn (NPH) will be provided and reviewed during the telephone call (on or before Day –10) discussed below.

All patients who are currently using either a CSII pump or receiving MDI and are eligible to participate in the study based on the results of the screening procedures (within 28 days of Day -1 of Period 1) will be contacted via a telephone call on or before Day -10. This telephone call will confirm their eligibility and address any questions participants and parents/guardians may have about the upcoming test meal visits. Patients entering the study on CSII therapy will remain on their current basal rate and bolus settings during the lead-in period and will be instructed to bring additional pump supplies when they arrive at the study site.

Those patients receiving MDI and who will transition from their basal insulin to twice daily NPH insulin will review the site-provided instructions during this call. The investigator will ensure the patients are provided with NPH as required. Patients or their parents/guardians may call the site at any time to address questions or concerns as they arise (including, but not limited to the transition phase). In lieu of a telephone call on or before Day -10 to review insulin transition instructions, a site visit may be scheduled at the investigator's discretion.

This study comprises of 2 parts: Part A and Part B. During Part A, patients will receive a single dose of LY900014 and Humalog on 1 occasion each as SC bolus injection and in Part B a single dose of LY900014 and Humalog on 1 occasion each as SC bolus via CSII.

Patients will be randomised on Day 1 of Period 1 in Part A and Day -1 of Period 1 in Part B. For each age group, patients will be randomised to 1 of the 2 treatment sequences (first double-blind LY900014 then double-blind Humalog, and first double-blind Humalog then double-blind LY900014) in 1:1 ratio. In both parts, dosing in Period 1 and Period 2 can occur on consecutive days but not more than 22 days apart. For patients available for dosing on consecutive days, the medical assessments scheduled for Day -1 of Period 2 may be done on Day 1 of Period 1. Patients will undergo a rescreening visit if dosing visit between Part A and Part B is more than 28 days apart. Patients who participate in Part A may continue to Part B; however, patients who complete Part A but discontinue prior to Part B may be replaced by newly enrolled patients in Part B. Newly enrolled patients will be randomised to 1 of 2 treatment sequences after completing the screening per the Schedule of Activities (Section 2) and are expected to complete

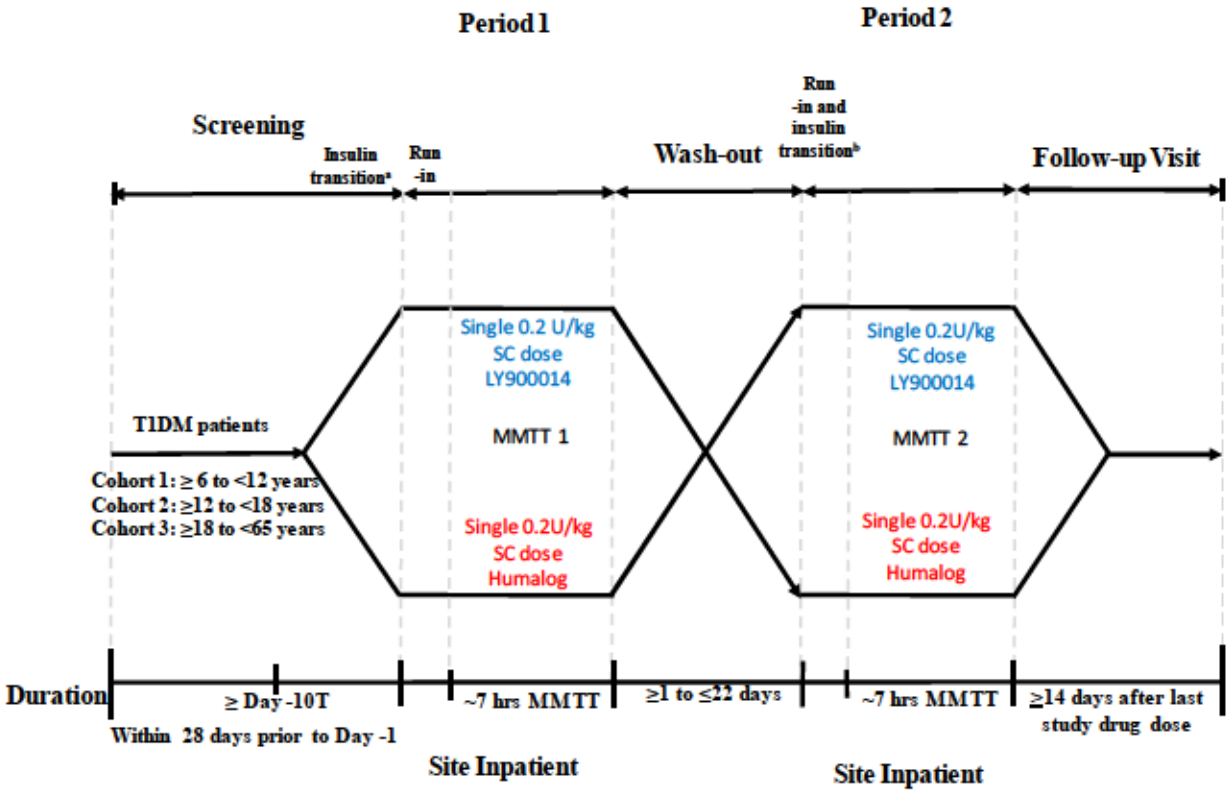
only Part B activities. Before each MMTT, a run-in period to stabilise blood glucose will occur. Details of run-in activities are described in Section 5.1.1.1, 5.1.2.1, and in Section 2.

A formal interim analysis is planned when all patients complete Part A (Section 10.3.5). Lilly intends to complete Part A to inform study design of the paediatric Phase 3 study. Initiation of Part B of the study may begin pending review of the PK, GD, safety, and tolerability data from Part A and ongoing or planned adult CSII Phase 1b studies.

5.1.1. Part A

In each period, patients will undergo an overnight run-in period followed by an MMTT (see Section 5.1.1.1). Each patient will receive single 0.2 U/kg of body weight SC injections of LY900014 and Humalog. The study drug will be administered immediately before the start of a test meal (see Section 6.3.1) per the assigned treatment sequence. This dose of insulin before the MMTTs for each patient will be the same for each test meal throughout the crossover periods; this dose will also be maintained for the patient in Part B.

Figure ITSA.1 illustrates the study design for Part A.



Abbreviations: MDI = multiple daily injection; MMTT = mixed meal tolerance test; NPH = neutral protamine Hagedorn; SC = subcutaneous; T = telephone visit; T1DM = type 1 diabetes mellitus.

a At study entry, patients on MDI therapy with any basal insulin other than NPH twice daily will transition to NPH twice daily therapy approximately 7 to 3 days prior to Day -1 of Period 1.

b Insulin transition is applicable if Period 2 occurs >3 to 7 days after Period 1.

The second MMTT assessment may occur on consecutive days but no more than 22 days after the first MMTT.

Figure ITSA.1. Illustration of study design for Part A.

Patients will be required to attend the study site on 3 or 4 occasions for Part A as described below:

- A screening visit (up to 28 days prior to Day -1 of Period 1). The informed consent/assent will be obtained during this visit and patients will be provided a diary to document any AEs and/or hypoglycaemic events. A telephone visit is planned after screening and on or prior to Day -10 to inform patients of their eligibility, provide instructions and address any questions participants and parents may have about the upcoming test meal visits.
- Two separate inpatient overnight stays from Day –1 to Day 1 (1 in each study period for MMTTs). These inpatient stays may occur on consecutive nights.
- A follow-up visit at least 14 days after the last dose or early discontinuation if the patient discontinues after Part A.

Patients will be discharged from the study site on Day 1 (at least 7 hours after the test meal) or later, if deemed necessary for safety monitoring as determined by the investigator.

Patients entering the study on MDI therapy with any basal insulin other than NPH twice daily will transition to NPH twice daily therapy approximately 7 to 3 days prior to Day -1 of Period 1. Transition guidelines, including dosages and timing, will be determined by the investigator and will be based on the needs of individual patient.

On Day -1, the last injection of NPH prior to the MMTT will occur in the morning and will resume only after the completion of the MMTT assessment (~7 hours postdose on Day 1).

5.1.1.1. Inpatient Procedures for Part A

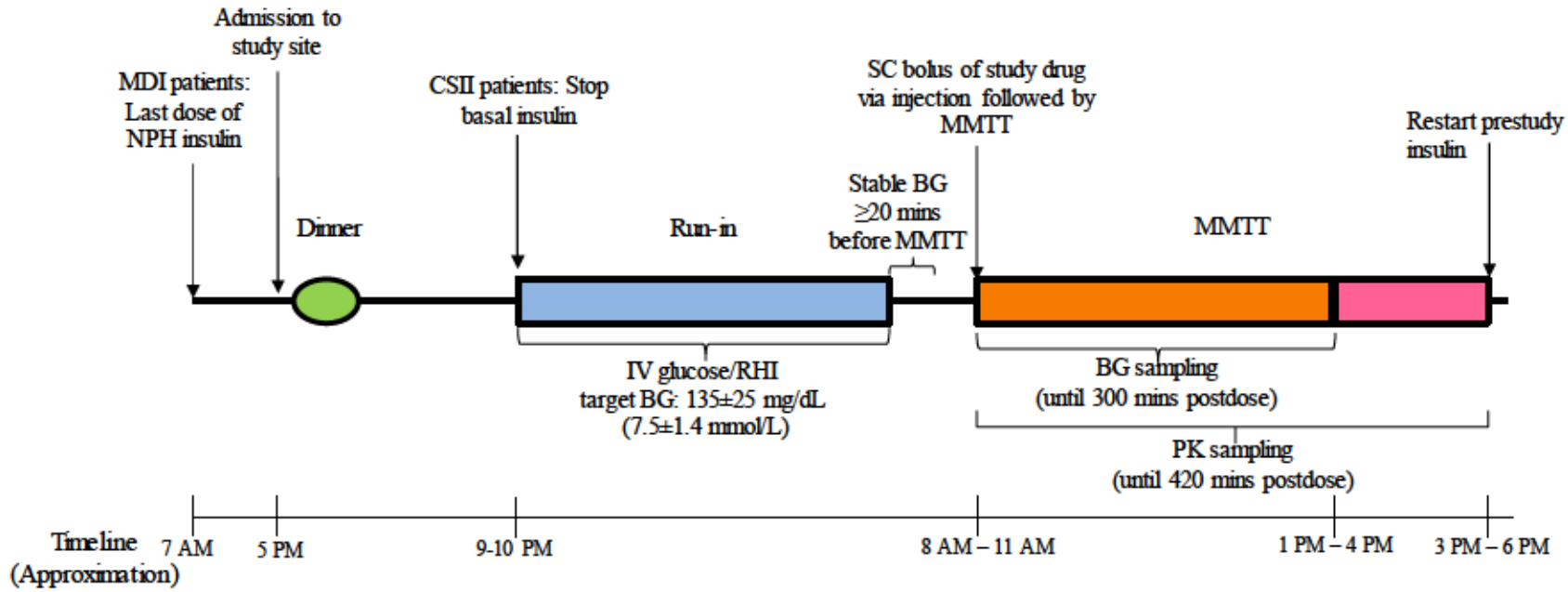
On the day before each MMTT day (i.e., Day –1 in each of the 2 periods), patients will arrive at the study site in the early evening (approximately 05:00 PM). The patient's short-acting insulin will be administered before the start of a standardised dinner. Before the start of a run-in period, the cannulation of the vein will be performed. At the start of the run-in period, patients entering the study on CSII therapy will suspend all insulin delivery and disconnect tubing from the infusion site.

Start of the run-in period will occur following the evening meal (approximately at 09:00 or 10:00 PM). The run-in period will start with a variable IV infusion of glucose (5% dextrose solution) or RHI to reach a target glucose level of 135±25 mg/dL (7.5±1.4 mmol/L). If this target glucose level is not attained before 11:00 AM on Day 1, MMTT will be halted and may be performed on a separate visit; an MMTT can only be rescheduled (up to 7 days) once for each study period. During the run-in period, blood glucose concentrations will be monitored at a minimum of 30- to 60-minute intervals (see Sections 7.4.1 and 9.6.1).

The run-in period will end once the target blood glucose level is attained and remains stable without intervention for at least 20 minutes before the scheduled start time of MMTT on Day 1. The MMTT will start in the early morning at approximately 08:00 AM with allowance up to 11:00 AM, if required, to ensure the patient's blood glucose is stable and on target, with the premeal activities as specified in the Schedule of Activities (Section 2). LY900014 or Humalog SC bolus injection will be administered immediately before the start of MMTT using an insulin syringe. The liquid test meal will be administered on Day 1 for each of the 2 treatment periods. A detailed description of the test meal is presented in Section 6.3.1. Patients are expected to complete each test meal within 15 minutes of starting the meal. Patients will be without further oral food intake following consumption of liquid test meal to completion of blood glucose collection (approximately 300 minutes) unless required to treat hypoglycaemia, as defined by the PG level ≤70 mg/dL (3.9 mM) with symptoms or any PG ≤60 mg/dL (3.0 mM) during the inpatient period, i.e., reversed with either rapidly absorbable oral carbohydrates or IV glucose. If a patient's blood glucose concentration rises above 300 mg/dL (16.7 mM) for more than 1 hour, RHI will be administered IV. In both cases, blood samples for blood glucose (for safety) will be taken and PK samples will be collected as planned. For each MMTT, the patient should stay in a sitting or semisupine position for 2 hours postdose and the patient will not be allowed to consume water for 2 hours after dosing (see Figure ITSA.2). If necessary, patients may be given

a low carbohydrate snack (<20 g carbohydrate), which does not require an insulin dose, after GD assessments (approximately 300 minutes postdose). Following completion of the assessment period and sample collection (approximately 420 minutes), patients will be offered a meal. For patients who were using MDI therapy, the investigator shall provide guidance on whether they should resume their prestudy basal insulin at the end of Period 1 or continue with NPH depending on the length of time between Period 1 and Period 2. Patients may return to pre-study basal insulin following completion of Period 2 MMTT sampling period with investigator's guidance. For CSII patients, the insulin pump may be resumed at the usual rates and settings with prestudy insulin and bolus mealtime insulin will be administered. A new infusion set may be required.

Patients will be observed following administration of the meal and discharged at the investigator's discretion.



Abbreviations: BG = blood glucose; CSII = continuous subcutaneous insulin infusion; IV = intravenous; MDI = multiple daily injection; MMTT = mixed meal tolerance test; NPH = neutral protamine Hagedorn; PK = pharmacokinetics; RHI = regular human insulin; SC = subcutaneous.

Figure ITSA.2. Inpatient procedure in Part A.

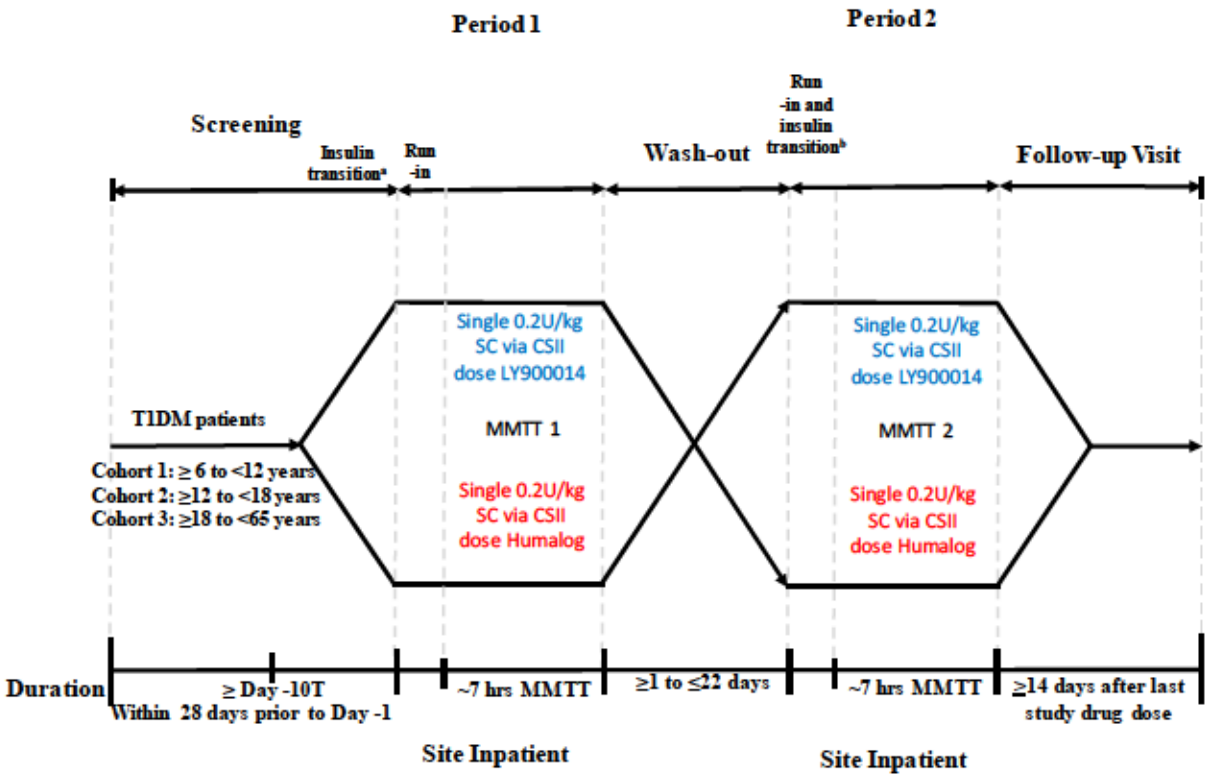
Assessment of local tolerability at all injection sites will be performed as specified in the Schedule of Activities (Section 2), including inspection of the injection/catheter site for signs such as oedema, erythema, and rash.

5.1.2. Part B

Patients who completed Part A but discontinued before the beginning of Part B may be replaced by newly enrolled patients in Part B. Newly enrolled patients will be randomised to 1 of 2 treatment sequences after completing the screening per the Schedule of Activities (Section 2) and are expected to complete only Part B activities.

Patients will receive either LY900014 or Humalog with an insulin lispro dose level of 0.2 U/kg body weight, as a SC bolus dose delivered using the CSII pump per the assigned treatment sequence. Patients will receive the assigned treatment immediately before each of the test meals. At the start of dosing period (Day 1), a standardised test meal will be administered (see Section 6.3.1).

Figure ITSA.3 illustrates the study design for Part B.



Abbreviations: CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injection; MMTT = mixed meal tolerance test; NPH = neutral protamine Hagedorn; SC = subcutaneous; T = telephone visit; T1DM = type 1 diabetes mellitus.

[a] Prior to Period 1, patients on MDI therapy with any basal insulin other than NPH twice daily will transition to NPH twice daily therapy approximately 7 to 3 days prior to Day -1 of Period 1.

[b] Insulin transition is applicable if Period 2 occurs >3 to 7 days after Period 1. The second MMTT assessment may occur on consecutive days but no more than 22 days after the first MMTT.

Figure ITSA.3. Illustration of study design for Part B.

Patients will be required to attend the study site on 3 to 4 occasions for Part B:

- A screening visit (may occur up to 28 days prior to Day -1 of Period 1). The informed consent/assent will be obtained from newly enrolled patients during this visit and a diary will be provided to document any AEs and/or hypoglycaemic events. The informed consent/assent is not applicable to patients continuing from Part A.
- A telephone visit is planned after screening and on or before Day -10 to inform patients of their eligibility and address any questions participants and parents may have about the upcoming test meal visits.
- Two separate inpatient overnight stays from Day –1 to Day 1 (1 in each study period for MMTTs). These inpatient stays may occur on consecutive nights.

- A follow-up visit at least 14 days after the last dose or early discontinuation.

Patients will be discharged from the study site on Day 1 (at least 7 hours after the test meal) or later, if deemed necessary for safety monitoring as determined by the investigator.

Patients entering the study on MDI therapy with any basal insulin other than NPH twice daily will transition to NPH twice daily therapy approximately 7 to 3 days prior to Day -1 of Period 1. On Day -1, the last injection of NPH prior to the MMTT will occur in the morning and will resume only after the completion of the MMTT assessment (~7 hours postdose on Day 1).

5.1.2.1. Inpatient Procedures for Part B

On the day before each MMTT day (i.e., Day –1 in each of the 2 periods if performed on non-consecutive days), patients will arrive at the study site in the early evening (approximately 05:00 PM). Patients on CSII pump will be advised to bring a spare infusion set for the CSII pump when they arrive at the study site. Patients who are not using CCI pump will be switched to a CCI pump during the inpatient procedures. A standardised dinner will be provided where the bolus dose of the patient's usual insulin will be administered via CSII for this meal. Patients on MDI will be started on CCI pump following the evening meal. The pump reservoir will be filled with the study insulin, either LY900014 or Humalog, and a new standard infusion set and catheter will be inserted after a priming dose has been given to test the catheter. In case of immediate infusion set intolerance, a new needle can be inserted up until 12:00 AM (midnight). Following the evening meal, patients will continue their current pump basal rate until the start of the run-in period at which time a fixed low basal rate of 0.1 U/hour will be maintained until 2 hours before the scheduled start time of MMTT. For patients transitioning from MDI therapy, the bolus dose used for the evening meal will be based on their usual insulin to carbohydrate ratio and correction factor if applicable. Additionally, the basal insulin rate for the period between dinner and the start of the overnight infusion should be determined using the 80% of the pre-study total daily NPH dose divided by 24 hours to obtain the hourly basal insulin infusion rate. The new basal rate may be titrated as needed based on the investigator's discretion. Before the start of a run-in period, the cannulation of the vein will be performed. Start of the run-in period will occur following the evening meal (at approximately 09:00 or 10:00 PM). The run-in period will start with a variable IV infusion of glucose (5% dextrose solution) or RHI to reach a target glucose level of 135±25 mg/dL (7.5±1.4 mmol/L). If this target glucose level is not attained before 1100 hours on Day 1, MMTT will be halted and may be performed on a separate visit; an MMTT can only be rescheduled (up to 7 days) once for each study period. During the run-in period, blood glucose concentrations will be monitored at a minimum of 30- to 60-minute intervals.

The run-in period will end once the target blood glucose level is attained and remains stable without intervention for at least 20 minutes immediately before the scheduled start time of MMTT on Day 1. The MMTT will start in the early morning at approximately 08:00 AM with allowance up to 11:00 AM, 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 or Humalog SC bolus will be administered immediately before the start of MMTT via the pump. The liquid test meal will be administered on Day 1 for each of the 2 treatment

periods. A detailed description of the test meal is presented in Section 6.3.1. Patients are expected to complete each test meal within 15 minutes of starting the meal. Patients will be without further oral food intake following consumption of liquid test meal to completion of blood glucose collection (approximately 300 minutes) unless required to treat hypoglycaemia, as defined by the PG level ≤70 mg/dL (3.9 mM) with symptoms or any PG ≤60 mg/dL (3.0 mM) during the inpatient period, i.e., reversed with either rapidly absorbable oral carbohydrates or IV glucose. If a patient's blood glucose concentration rises above 300 mg/dL (16.7 mM) for more than 1 hour, RHI will be administered IV. In both cases, blood samples for blood glucose (for safety) will be taken and PK samples will be collected as planned. For each MMTT, the patient should stay in a sitting or semisupine position for 2 hours postdose and the patient will not be allowed to consume water for 2 hours after dosing. If necessary, patients may be given a low carbohydrate snack (<20 g carbohydrate), which does not require an insulin dose, after GD assessments (approximately 300 minutes postdose). If Period 2 is performed on non-consecutive days, following completion of the assessment period and sample collection (approximately 420 minutes), the pump will be disconnected. For patients who used CSII pre-study, a new reservoir should be filled with their usual pump insulin and a new infusion set should be inserted as directed by the study site. The basal rates may be returned to the patient's usual basal settings (see Figure ITSA.4).

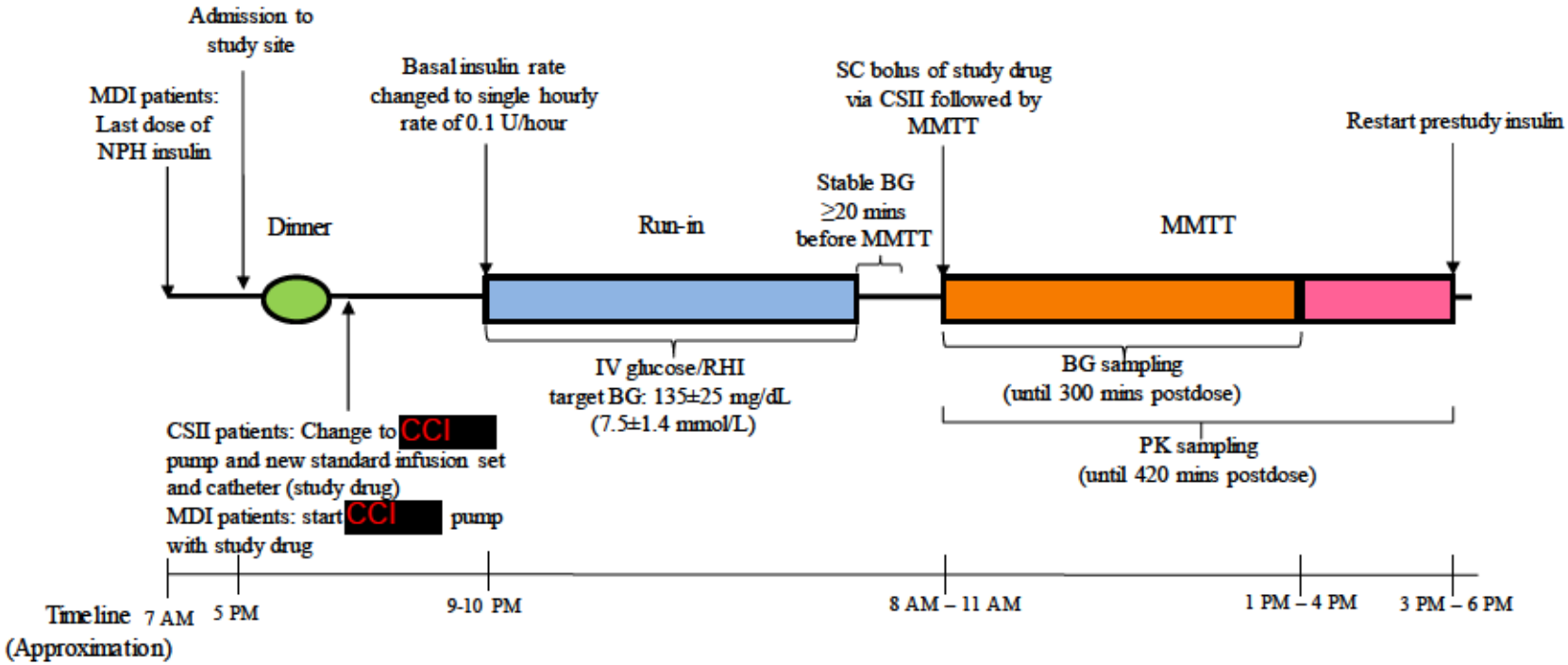
For patients who were using MDI therapy, the investigator shall provide guidance on whether they should resume their pre-study basal insulin at the end of Period 1 or continue with NPH depending on the length of time between Period 1 and Period 2.

All patients will be offered a meal at the conclusion of the MMTT assessment period.

For patients who opt to complete Period 2 on consecutive days, the pump reservoir will be filled with the other study insulin, either LY900014 or Humalog, and a new standard infusion set and catheter will be inserted prior to administration of the evening meal. In case of immediate infusion set intolerance, a new needle can be inserted up until 12:00 AM (midnight). A standardised dinner will be provided where the bolus dose for this meal will be administered via CSII. Following the evening meal, patients will continue their current pump basal rate until the start of the run-in period at which time a fixed low basal rate of 0.1 U/hour will be maintained until 2 hours before the scheduled start time of MMTT. A similar approach to that used in Period 1 will be used to manage the evening meal bolus, the run-in period, overnight basal insulin infusion, administration of study insulin bolus, and conduct of the MMTT. At the end of the MMTT assessment period, patients who used CSII pre-study should fill a new reservoir with their usual pump insulin and a new infusion set should be inserted as directed by the study site. The basal rates may be returned to the patient's usual basal settings. Patients previously treated with MDI therapy should resume their pre-study MDI therapy at the end of Period 2 as directed by the site. All patients will be offered a meal at the conclusion of the MMTT assessment period. Patients will be observed following administration of the meal and discharged at the investigator's discretion.

Assessment of local tolerability at all injection sites will be performed as specified in the Schedule of Activities (Section 2), including inspection of the injection/catheter site for signs such as oedema, erythema, and rash.

For each inpatient visit, serial blood samples will be collected over approximately 420 minutes to assess the PK and GD response following the start of each test meal.



Abbreviations: BG = blood glucose; CSII = continuous subcutaneous insulin infusion; IV = intravenous; MDI = multiple daily injection; MMTT = mixed meal tolerance test; NPH = neutral protamine Hagedorn; PK = pharmacokinetics; RHI = regular human insulin; SC = subcutaneous.

Figure ITSA.4. Inpatient procedure in Part B.

5.2. Number of Participants

Approximately 45 patients may be enrolled into the study so that approximately 36 patients (12 patients in each age group [6 to <12 years, 12 to <18 years, and 18 to <65 years] based on the age at initial screening) complete both inpatient periods in both the parts of the study.

Patients participating in Part A may continue participation in Part B. If patients from Part A decline participation in Part B or drop out from Part A, additional patients will be enrolled to ensure approximately 36 patients (12 patients in each age group) complete both periods in Part B of the study.

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

Each study part consists of a 2-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 for a crossover design is less than the number needed for a parallel group design.

Randomisation and blinding are used to avoid bias introduced through an association between allocation order of study drug and patient characteristics.

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 will allow for improved comparability of the postprandial glucose response to a mixed meal after treatment with LY900014 and Humalog administered immediately before the start of the 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. Regular human insulin has been chosen for the IV optimisation of PG during the run-in because RHI does not cross-react with the insulin lispro–specific assay used for the PK analysis.

5.5. Justification for Dose

The bolus dose of insulin lispro (LY900014 or Humalog) will be fixed dose by body weight (0.2 U/kg). Based on previous studies of both insulin lispro (Humalog) and LY900014, a 0.2 U/kg prandial dose is necessary to provide measurable PK and GD profiles for both study insulins. This dose level has been previously examined in paediatric patients with another rapid-acting analogue with no apparent hypoglycaemic risk (Fath et al. 2017). Furthermore, the occurrence of hypoglycaemia in patients with T1DM or T2DM participating in previous test meal studies with LY900014 was also low, since patients do not receive significant basal insulin coverage during the course of the MMTT.

Meal size differs between adults and children. Due to this, the volume of the liquid test meal for the MMTT will be adjusted by weight for the child and adolescent patients within the study. However, the adult patients in the study will receive a set volume for the MMTT.

For each patient, the individualised prandial insulin lispro dose in LY900014 and Humalog for each test meal must be kept identical throughout the crossover periods for both Part A and Part B. If the investigator determines that it would be unsafe to repeat the same dose, the patient should be discontinued. A minimum weight of 25 kg is required for this study in order to have sufficient dose CCI to characterise both the serum insulin lispro absorption and elimination following study drug administration.

6. Study Population

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

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to Day -1 of Period 1 for both Part A and Part B. Patients who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

[1] male or female patients with a diagnosis of T1DM based on medical history for at least 1 year as previously demonstrated by either documented presence of autoimmune antibodies (glutamic acid decarboxylases; insulin-associated tyrosine phosphatase antibody; insulin autoantibody; islet cell antibody) as per medical records, or diagnosis by an endocrinologist (paediatric or adult).

[1a] no male contraception required except in compliance with specific local government requirements

[1b] female patients:

i. Post-pubertal females are defined as children and adolescents ≥12 years of age or <12 years of age who have onset of menses

ii. Post-pubertal females 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.

iii. Otherwise, post-pubertal females of child-bearing potential participating must agree to use 1 highly effective method of contraception for the entirety of the study.

1. Post-pubertal females 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.

2. One highly effective method of contraception. The patient may choose to use 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.

iv. post-pubertal females not of child-bearing potential may participate and include those who are

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

2. post-menopausal – defined as no menses for 12 months without an alternative medical cause. A follicle-stimulating hormone 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 ≥6 and <65 years

[3] children and adolescents have a body mass index (BMI) within the 3rd and 95th BMI percentiles with a minimum weight of 25 kg; adults have a BMI ≤28.0 kg/m^2

[4] continuous treatment with insulin for at least 12 months and with at least 6 months of treatment using CSII pump therapy or MDI therapy consisting of treatment with basal insulin (including insulin glargine U100, detemir, degludec U100 and NPH) and rapid-acting insulin prior to the main meals of the day before screening

[5] total daily dose of insulin between 0.3 and 1.5 U/kg/day, inclusive

[6] have a glycated haemoglobin (HbA1c) ≤10% at screening

[7] compliant with prescribed diet and insulin therapy, as determined by the investigator

[8] have clinical laboratory test results within normal reference range (with the exception of HbA1c) for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

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

[10] are reliable and willing to make themselves/their wards available for the duration of the study and are willing to follow study procedures

[11] are able and willing to give signed informed consent approved by Lilly and the ethical review board (ERB) governing the site or both the child/adolescent and a parent or legal guardian are able to understand and fully participate in the activities of the clinical trial and sign their assent and consent, respectively

6.2. Exclusion Criteria

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

[12] receiving any oral or injectable medication intended for the treatment of diabetes mellitus other than insulins in the 12 months prior to screening

[13] more than 1 episode of severe hypoglycaemia (defined as requiring assistance due to neurologically disabling hypoglycaemia, indicated by coma or convulsion and/or use of IV glucose or glucagon) within 6 months prior to screening

[14] two or more emergency room visits or hospitalisations due to poor glucose control (hyperglycaemia or diabetic ketoacidosis) within 6 months of screening

[15] post-pubertal females not using a reliable method of birth control, or intending to become pregnant

[16] one of the following concomitant diseases: presence of clinically significant hematologic, oncologic, renal, cardiac, hepatic, or gastrointestinal disease, proliferative retinopathy, uncontrolled celiac disease, uncontrolled hyperthyroidism or hypothyroidism, or adrenal insufficiency

[17] 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]) (Schwartz et al. 2009).

[18] hepatic: Have obvious clinical signs or symptoms of liver disease (e.g., acute or chronic hepatitis as indicated by evidence and/or positive antibody/surface antigen to hepatitis B/C, or cirrhosis) or elevated liver enzyme measurements as indicated below at screening:

a. total bilirubin level (TBL) ≥2× the upper limit of normal (ULN) (with the exception of Gilberts disease) as defined by the central laboratory,

   OR

b. alanine aminotransferase (ALT) ≥3× ULN as defined by the central laboratory

   OR

c. aspartate aminotransferase (AST) ≥3× ULN as defined by the central laboratory

[19] are study 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

[20] are Lilly employees or are employees of the study site and their children

[21] 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

[22] have participated, within the past 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life ($t_{1/2}$), 5 half-lives or 30 days (whichever is longer) should have passed

[23] have previously completed or withdrawn from this study

[24] have known allergies to treprostinil CCI insulin lispro, RHI, related compounds, or any components of the formulation, or a history of significant atopy

[25] Adults ≥18 years of age who have donated blood of more than 450 mL or more in the past 3 months before screening or

any prospective study participant who has experienced severe blood loss within 3 months prior to screening or have known haemoglobinopathy, haemolytic anaemia, or sickle cell anaemia, or any other traits of haemoglobin abnormalities known to interfere with the HbA1c measurement

[26] receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, and inhaled preparations) or have received such therapy within 8 weeks immediately before screening

[27] 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

[28] have a history of in-patient psychiatric treatment, emotional, behavioural, or other untreated conditions that would interfere with proper participation in routine diabetes control and management in the past 6 months

[29] 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

[30] have, except for current regimen of insulin therapy and concomitant medication(s) (e.g., 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

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

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

[33] are women who are lactating

[34] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption for the duration of the study
(1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[35] are unable to comply with smoking restrictions during the study

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

6.2.1. Additional Exclusion Criteria for Inpatient Dosing Days

[37] consumption of alcohol within 24 hours prior to admission

[38] positive serum pregnancy test at screening or positive urine pregnancy test at admission to the study site

[39] consumption of coffee, tea, chocolate, cola, and/or energy drinks containing methyl xanthine (caffeine, theophylline, or theobromine) within 12 hours before each test meal assessment.

[40] strenuous exercise within the past 24 hours before each test meal assessment

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

[42] any use of excluded prescription or nonprescription medication from 14 days prior to dosing and throughout the study

[43] hypoglycaemia during the MMTT period and less than 24 hours before dosing that poses a significant risk to patient's safety, as judged by the investigator

[44] injection of a bolus of more than 6 U of a fast-acting insulin analogue 6 hours before dosing prior to the test meal

6.2.2. Rationale for Exclusion of Certain Study Candidates

The blood volume to be withdrawn per patient in each part of this study is approximately 170 mL which would be a challenge in children <6 years of age. Additionally, insulin is individually titrated and therefore, the understanding of PK and GD in the proposed patients (≥6 years to ≤64 years) should be sufficient to inform dosing in children <6 years of age under the supervision of a qualified endocrinologist. Therefore, this study will not include paediatric patients with T1DM from birth to <6 years of age.

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 provided standardised liquid meals for the MMTTs, as outlined in the Schedule of Activities (Section 2). An evening meal on the day prior to the MMTT and a meal following completion of the MMTT will also be provided. Patients will be fasted (except for water) for at least 10 hours before each test meal and consume each meal within approximately 15 minutes. The standardised liquid test meal will use CCI [redacted] For children and adolescents in the study, the volume of the liquid test me [redacted] ed on the patient's body weight (kg) during the study (Period 1 of Part A or Period 1 of Part B if patients did not participate in Part A of the study) as described in Table ITSA.2. For adults, the liquid test meal will consist of CCI [redacted] approximately 100 g of carbohydrates total in test meal). [redacted] pt consistent with regard to calorie and nutrient content across all MMTT assessments in the study. For both parts of the study, the patient will not be allowed to consume water for 2 hours after dosing apart from fluid provided with the meal; however, water may be consumed freely afterwards.

Table ITSA.2. Volume of Standardised Meal According to Body Weight

Body Weight (kg)	Volume of Meal (mL)
25-29	230
30-34	272
35-39	315
40-44	357
45-49	400
50-54	442
>55	474 CCI [redacted]

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

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

6.3.2. Caffeine, Alcohol, and Tobacco

Patients should refrain from caffeine-containing food/beverages (e.g., 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 study site visit, excluding the test meal when CCI [redacted] may be given.

No alcohol will be allowed at least 24 hours before each study site admission (Day –1) and throughout the duration of each study site visit. Between study site visits, daily alcohol consumption should not exceed 21 units per week for males and 14 units per week for females.

No cigarette smoking will be permitted during the inpatient visits.

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once. The interval between re-screenings should be at least 28 days. Each time re-screening is performed, a new informed consent or assent form (see Appendix 3 for details) must be signed and participants will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY900014 and Humalog administered either SC (Part A) or via CSII (Part B). Table ITSA.3 shows the treatment regimens.

Table ITSA.3. Treatments Administered

Treatment Name	LY900014	Humalog
Dose Strength	100 U/mL	100 U/mL
Route of Administration	SC or CSII	SC or CSII

Abbreviations: CSII = continuous subcutaneous insulin infusion; SC = subcutaneous.

The investigator or designee is responsible for

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

Each dose of study drug will be prepared by the investigator or designee and treatments will be administered using an insulin U-100 SC in Part A or via CCI CSII bolus in Part B. The rate of bolus infusion in Part B will be standardised to 0.1 U/hour during the run-in period. Each insulin vial will be labelled appropriately and dispensed to qualified study site personnel for administration. All study drugs will be given through SC injection (Part A) or via a CCI CSII pump (Part B) at the study site by qualified and appropriately trained site personnel as designated by the investigator. For SC administration, an appropriate size of needle shall be used to ensure all injections are delivered to a consistent target depth into the SC space; if an 8-mm (or greater) needle is used to administer the injection, the skinfold should be pinched. The CSII infusion set and stainless steel catheter should be inserted at a 90° angle in the abdominal area.

Injections will be rotated among different injection sites on the anterior abdominal wall during the 2 study periods (i.e., left lower quadrant and right lower quadrant). Study injections should be given by a limited number of individuals for consistency.

7.1.1. Packaging and Labelling

The study insulin (LY900014 and Humalog) will be provided to the study site in blinded vials. All clinical study materials 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 study drugs will be fully documented and verified by a second person. Detailed records of the amounts of the study drug received, dispensed, and remaining at the end of the study will be maintained.

Regular human insulin will be provided by Lilly and will be used from their original packaging.

The study drug will be labelled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrolment will be randomised to 1 of the 2 treatment sequences on Period 1 Day 1 for Part A and Period 1 Day -1 for Part B. Assignment to treatment sequences will be determined by a computer-generated random sequence using an interactive web response system (IWRS). Patients will be randomised to 1 of the 2 treatment sequences in 1:1 ratio within each age group (first double-blind LY900014 then double-blind Humalog, and first double-blind Humalog then double-blind LY900014). The randomisation in Part A and Part B is determined separately. Patients participating in both Part A and Part B will be randomised at the beginning of each part. Patients participating in only Part B will be randomised at the beginning of Part B.

7.2.1. Selection and Timing of Doses

The SC injection dose and bolus dose via CSII of insulin (LY900014 and Humalog) will be 0.2 U/kg body weight to cover the carbohydrate content of the standardised liquid test meal. The insulin dose will be determined from the body weight in Period 1 of Part A or Period 1 of Part B if patients did not participate in Part A of the study. This insulin dose (U) of LY900014 and Humalog for each patient must be used for the test meals throughout the crossover periods in Part A and Part B. The same total dose will be administered to a particular patient in both parts of the study and if the investigator determines it would be inappropriate to administer this dose, the patient will be discontinued from the study.

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

7.3. Blinding

The study is patient- and investigator-blind with reference to the identity of the study drug administered, and the study drug vials will be blinded.

A limited number of study team members (not involved in the practical execution of the clinical study or the collection of data at the study site), will have access to the unblinded treatment assignments and data as described in the blinding plan.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labelling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the IWRS.

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 subject'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.

7.4. Dose Modification

Dose adjustments are not allowed during the study MMTT procedure.

7.4.1. Special Treatment Considerations

Regular human insulin and 5% dextrose solution will be used during the run-in period to stabilise blood glucose prior to the start of the meal test. Regular human insulin may also be provided to treat hyperglycaemia during the meal test (see Section 9.4.6).

In an effort to minimise discomfort, the study site may use a topical anaesthetic cream prior to venipuncture for insertion of indwelling intravascular catheter to obtain blood samples, thus limiting the number of needle insertions directly into patients' skin. Additionally, the number of blood samples has been reduced with a total blood volume of less than 200 mL to be collected in each part (Parts A and B).

7.5. Preparation/Handling/Storage/Accountability

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

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

The study drugs must be stored at the study site under refrigerated conditions (between 2°C and 8°C) in a locked and secure place. Insulin must not be frozen.

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

7.6. Treatment Compliance

The study drug will be administered at the study site, and documentation of treatment administration will occur at the study site.

7.7. Concomitant Therapy

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

In general, the addition of new concomitant medication should be avoided; however, paracetamol, or other over-the-counter analgesics may be administered at the discretion of the investigator based on age appropriate dosing guidelines for treatment of headache, 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 CP or clinical research physician (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 AE and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation from the study and the study drug for abnormal liver test results will occur after consultation between the investigator and the Lilly-designated medical monitor if a patient meets 1 of the following conditions:

- ALT, AST >8X ULN
- ALT or AST >5X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and TBL >2X ULN or international normalised ratio >1.5 or
- ALT or AST >3X ULN and the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

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

8.2. Discontinuation from the Study

Patients will be discontinued under the following circumstances:

- Enrolment in any other clinical study involving an study drug or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator decision
    - 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 an abnormal clinically significant laboratory value, or in the case of severe hypo- or hyperglycaemic episode (see Section 9.4.5.2 and 9.4.6)
- Patient decision

- the patient, or the patient's parents or guardian, requests to be withdrawn from the study

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

8.3. Patients Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The study 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 study site.

9. Study Assessments and Procedures

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

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

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study drug or the study, or that caused the patient to discontinue the study drug before completing the study. The patient should be followed up until the event resolves, stabilises with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form (ICF) is signed, study site personnel will record, via electronic data entry, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, study 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 drug, 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 study drug, 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 study drug is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry.

Hypoglycaemic events are AEs of special interest and will be collected and reported throughout the study as described in Section 9.4.5.2. All hypoglycaemic events will be recorded in the hypoglycaemia module in the eCRF allowing for the collection of comprehensive safety information relating to these events.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalisation
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above
- when a condition related to the CSII pump 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.

The 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 electronic data entry after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received the study drug. However, if an SAE occurs after signing informed consent, but prior to receiving the study drug, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued from and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has

been discharged from the study, and he/she considers the event reasonably possibly related to the study drug or study participation, the investigator must promptly notify Lilly.

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

Lilly collects product complaints on study drugs 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 study drug or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY900014 or Humalog is considered any dose higher than the dose assigned on Day 1 of Part A.

Excess insulin administration may cause hypoglycaemia and hypokalaemia. Mild episodes of hypoglycaemia usually can be treated with oral glucose. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/SC glucagon or concentrated IV glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery. Hypokalaemia must be corrected appropriately.

Refer to the IB and/or Humalog Product Label.

9.4. Safety

9.4.1. Laboratory Tests

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

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

9.4.2. Vital Signs

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

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

9.4.3. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the study drug should be reported to Lilly, or its designee, as an AE via eCRF.

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

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

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

9.4.4. Other Tests

9.4.4.1. Hip and Waist Circumference

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

9.4.4.2. Body Weight and Height

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

9.4.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- adverse events.

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

9.4.5.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated 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, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalise and/or are returning to approximate baseline levels.

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

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

9.4.5.2. Glucose Monitoring

Hypoglycaemia will be described using the following definitions (IHSG 2017):

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

- **Documented symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by PG <54 mg/dL (3.0 mmol/L)
- **Documented asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with PG <54 mg/dL (3.0 mmol/L)
- **Documented unspecified hypoglycaemia**: an event during which PG <54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded

- **Severe hypoglycaemia (Level 3):** an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the patient has an altered mental status and cannot assist in his/her own care, is semiconscious or unconscious, or experienced coma with or without seizures. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L])
  - **Severe hypoglycaemia in children:** because children have limited ability to detect and/or self-treat hypoglycaemia, severe hypoglycaemia in children is an event in which children have altered mental status, and cannot assist in their care, are semiconscious or unconscious, or in coma with or without convulsions, and may require parenteral therapy (glucagon or IV glucose)
  - **Severe hypoglycaemia requiring medical attention**: a severe hypoglycaemic event when patients require therapy by health care providers (emergency medical teams, emergency room personnel, etc.)

Other Hypoglycaemia:

- **Nocturnal hypoglycaemia:** any hypoglycaemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycaemia) that occurs at night and presumably during sleep
- **Relative hypoglycaemia:** an event during which typical symptoms of hypoglycaemia, which 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) hypoglycaemia:** this optional category combines all cases of hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, the event is counted only once in this category
- **Probable symptomatic hypoglycaemia:** an event during which symptoms of hypoglycaemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

9.4.5.3. Severe Hypoglycaemia

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

All hypoglycaemic events will be recorded in the eCRF. All episodes of severe hypoglycaemia must be reported as SAEs.

9.4.5.4. Injection-Site Assessments (Local Tolerability)

Injection-site (Part A) and catheter-site (Part B) 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/catheter 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/catheter site will be evaluated by means of the following objective and subjective assessments within the following categories: pain (including burning), itching, erythema, oedema, and induration/infiltration. The assessments will be recorded by the study site personnel.

9.4.6. Treatment of Hyperglycaemia and Hypoglycaemia

Patients will be without further oral food intake following consumption of liquid test meal to completion of blood glucose collection (approximately 300 minutes) unless required to treat hypoglycaemia, as defined by the PG level ≤70 mg/dL (3.9 mM) with symptoms or any PG ≤60 mg/dL (3.0 mM) during the inpatient period, i.e., reversed with either rapidly absorbable oral carbohydrates or IV glucose. If a patient's blood glucose concentration rises above 300 mg/dL (16.7 mM) for more than 1 hour, RHI will be administered IV. In both cases, blood samples for blood glucose (for safety) will be taken and PK samples will be collected as planned.

Patients may consume up to 20 g of carbohydrates to treat or prevent hypoglycaemia (<70 mg/dL [see Section 9.4.5.2]) during the fasting periods.

If a patient is experiencing hyperglycaemia (blood glucose concentration ≥300 mg/dL [16.7 mM]) during the MMTT for more than 1 hour, RHI will be administered IV.

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

9.5. Pharmacokinetics

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

9.5.1. Bioanalysis

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

Concentrations of insulin lispro will be assayed 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 study drug concentrations will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

The sample(s) will be stored until testing is completed and upon confirmation of results.

9.6.1. Glucodynamic Samples

Blood samples will be obtained for the measurement of glucose at the times specified in the Schedule of Activities (Section 2) using a point-of-care glucose meter that will be readily available at the study 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.

9.6.1.1. Glucose Samples (Run-In Period)

Blood glucose concentrations will be monitored at a minimum of 30- to 60-minute intervals during the run-in period on Day 1 through the use of fingerstick or an indwelling catheter to minimise discomfort to patients (see Section 7.4.1).

9.6.1.2. Glucose Samples (MMTT)

Blood samples will be obtained for the measurement of glucose at the times specified in the Schedule of Activities (Section 2) through the use of an indwelling catheter to minimise discomfort to patients. These glucose measurements will be used for patient safety management as well as for GD evaluations.

9.6.2. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro as specified in the Schedule of Activities (Section 2).

Immunogenicity will be assessed using a validated radio ligand-binding assay (RBA) to detect anti-insulin lispro antibodies in the presence of lispro. Instead of quantitating the level of anti-insulin lispro antibodies by titre, the RBA reports a semiquantitative percent-binding for each positive sample. Additionally, positive samples will be characterised for cross-reactive binding to native insulin.

Clinical and reliable on-market data indicate that the immunogenic potential of insulin lispro is comparable to other marketed insulins such as RHI (Fineberg et al. 1996) and, when present, anti-insulin antibodies do not appear to be clinically consequential (Fineberg et al. 2003). Therefore, rather than relying on an in vitro neutralisation assay, well-established in vivo measures of insulin lispro efficacy (i.e., insulin dose, HbA1c) may be utilised to directly monitor for any potential neutralising effect of anti-lispro antibodies.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY900014. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

Not applicable for this study.

9.8. Biomarkers

Not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The number of patients needed to complete either Part A or Part B of this study was pre-set to 12 in each age group (6 to <12 years, 12 to <18 years, and 18 to <65 years). Twelve completing patients in each age group will provide approximately 90% power to demonstrate 60% increase in the insulin lispro area under the plasma concentration-time curve from time zero to 30 minutes (AUC[0-30min]) between LY900014 and Humalog within each age group. The sample size will also provide greater than 85% power to demonstrate 30% reduction in time to early half-maximal drug concentration (early 50% t_{max}). The estimated standard deviation of within-subject difference on the log scale is 0.45 for AUC(0-30min) and 0.35 for early 50% t_{max}, according to an analysis of internal Lilly data and external published paediatric studies. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI).

Approximately 45 patients (approximately 15 patients in each age group) may be enrolled in the study to ensure approximately 36 patients complete both inpatient periods in both parts of the study. If patients complete Part A but decline participation in Part B or drop out from Part A, additional patients may be enrolled to ensure at least 36 patients complete Part B of the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

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

The analyses for Part A and Part B will be conducted separately using similar statistical methods. Primary statistical analyses will be conducted on the set of patients who complete both treatment periods. Supportive analyses may be done on the key parameters for the patients who complete at least one treatment period. Safety analyses will be conducted for the set of patients receiving at least 1 dose of the study drug, whether or not they completed all protocol requirements.

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented for continuous variables. Data from all 3 age groups will be pooled and analysed using a linear mixed-effect model for continuous variables unless otherwise stated in the succeeding subsections. The model will include treatment, sequence, period, age group, and the interaction of treatment and age group as fixed effects and patient within sequence as a random effect. The primary comparison between LY900014 and insulin

lispro for each age group will be based on the treatment difference or ratio of the given age group from the model.

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.

Any change in the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the study results.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All study drug- and protocol procedure-related AEs will be listed, and if the frequency of events allows, safety data (including hypoglycaemic events) will be summarised using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with study drug as perceived by the investigator. Symptoms reported to occur prior to enrolment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of study drug-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed, and may be summarised 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 receive at least 1 dose of study drug and have measurable insulin lispro concentrations will be included in the PK analysis dataset.

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

Free serum insulin lispro concentrations will be used to calculate several PK parameters, including early 50% t_{max}, time to late half-maximal drug concentration (late 50% t_{max}),

maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), half-life ($t_{1/2}$), and area under the plasma concentration time curve (AUC) from time zero to the last recorded time [AUC(0-tlast)], AUC from time zero to 30 minutes [AUC(0-30min)], AUC from time zero to 1 hour [AUC(0-1h)], AUC from time zero to 7 hours [AUC(0-7h)], and AUC from time zero to infinity [AUC(0-∞)]. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary.

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

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.

10.3.2.2. Pharmacokinetic Statistical Inference

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

The same model without log transformation will be used for the analysis of the PK time parameters (early 50% t_{max}, late 50% t_{max}, and t_{max}). Least-squares means (LSmeans), treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using the Fieller's theorem (Chow and Liu 2009).

10.3.3. Glucodynamic Analyses

10.3.3.1. Glucodynamic Parameter Estimation

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

Data will be analysed 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 (ΔAUC) from time 0 to 2 hours postmeal and ΔAUC from time 0 to 5 hours postmeal 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 after 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 for each age group and treatment.

10.3.3.2. Glucodynamic Statistical Inference

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented by treatment for each age group. The GD parameters on the original scale (not log transformed) will be analysed using the same model used for PK parameters. Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using the Fieller's theorem.

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

An interim analysis will be conducted after all patients complete Part A of this study to analyse the safety, PK, and GD data in order to support regulatory submission and future study design.

Data may be analysed while the trial is ongoing, but no changes to the study design are planned. Information that may unblind the study during the analyses will not be reported to study sites until the study has been unblinded. An assessment committee will not be formed.

11. References

Cengiz E. Undeniable need for ultrafast-acting insulin: the pediatric perspective. *J Diabetes Sci Technol*. 2012;6(4):797-801.

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

[DCCT] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.

EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet*. 2000;355(9207):873-876.

Fath M, Danne T, Biester T, Erichsen L, Kordonouri O, Haahr H. Faster-acting insulin aspart provides faster onset and greater early exposure vs insulin aspart in children and adolescents with type 1 diabetes mellitus. *Pediatr Diabetes.* 2017 Feb 6; doi: 10.1111/pedi.12506 [Epub ahead of print].

Fineberg NS, Fineberg SE, Anderson JH, Birkett MA, Gibson RG, Hufferd S. Immunologic effects of insulin lispro [Lys (B28), Pro (B29) human insulin] in IDDM and NIDDM patients previously treated with insulin. *Diabetes.* 1996;45(12):1750-1754.

Fineberg SE, Gulliya KS, Huang J, Anderson JH, Brunelle R. Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. *Diabetes Care.* 2003;26(1):89-96.

Humalog [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

Humalog: EPAR – Product Information. European Medicines Agency web site. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000088/WC500050328.pdf. Accessed August 14, 2017.

[IHSG] International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017 Jan;40(1):155-157.

Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, Bonnet D. Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. *J Pediatr*. 2011;158(4):584-588.

Lipman TH, Levitt Katz LE, Ratcliffe SJ, Murphy KM, Aguilar A, Rezvani I, Howe CJ, Fadia S, Suarez E. Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry. *Diabetes Care.* 2013;36(6):1597-1603.

Orenitram (treprostinil) [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; 2016.

Pettitt DJ, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, Liese AD, Linder B, Mayer-Davis EJ, Pihoker C, Sayday SH, Standiford DA, Hamman RF; SEARCH for Diabetes in Youth Study Group. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. *Diabetes Care*. 2014;37(2):402-408.

CCI

Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol.* 2009;4(11):1832–1843.

CCI

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation either will occur immediately after initial testing or will require that samples be held to be re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist

Term	Definition
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSII	continuous subcutaneous insulin infusion
ΔAUC	area under the baseline subtracted glucose concentration versus time curve
early 50% t_{max}	time to early half-maximal drug concentration
ECG	Electrocardiogram
eCRF	electronic case report form
enrol	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	US Food and Drug Administration
GCP	good clinical practice
GD	glucodynamic(s)
GFR	glomerular filtration rate
HbA1c	glycated haemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Term	Definition
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorised form, or marketed products used for an unauthorised indication, or marketed products used to gain further information about the authorised form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous(ly)
IWRS	interactive web response system
late 50% t_{max}	time to late half-maximal plasma concentration
legal representative	An individual or judicial or other body authorised under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
LSmeans	least-squares means
MDI	multiple daily injection
MMTT	mixed meal tolerance test
NPH	neutral protamine Hagedorn
PAH	pulmonary arterial hypertension
PG	plasma glucose
PK	pharmacokinetic(s)
randomise	The process of assigning subjects/patients to an experimental group on a random basis.
RBA	radio ligand-binding assay
RHI	regular human insulin
SAE	serious adverse event
SC	subcutaneous(ly)
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.
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life

Term	Definition
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
t_{max}	time of maximum observed drug concentration
U	Units
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

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

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

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

b Performed at screening only.

c eGFR will be calculated using relevant formulae (Schwartz et al. 2009).

d May be repeated prior to admission to the study site and at other times indicated in the Schedule of Activities.

e Females only, as indicated by the Schedule of Activities (see Sections 2 and 6.1 for more information).

f If clinically indicated, per investigator's discretion.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

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

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, participants below the age of 18 years will be required to provide their assent to this clinical trial. Age-appropriate information about this clinical trial will be provided to participants.

Recruitment

Study-specific recruitment material should be approved by Lilly.

Ethical Review

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

Documentation of ERB approval of the protocol, ICF and Assent Form 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 Insert or SPC and updates during the course of the study
- ICF and Assent Form

- relevant curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, 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 eCRF 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 study 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 Haematology[a]	**Haptoglobin[a]**
Haemoglobin	
Haematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear Antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth Muscle Antibody (or Anti-actin**
CPK	**Antibody)[a]**

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I8B-MC-ITSA Sampling Summary for Part A

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20	1	20
Clinical laboratory tests[a]	9	1	9
Pharmacokinetics – insulin lispro	1	21 samples x 2 periods = 42	42
Blood discard for cannula patency	1	21 samples x 2 periods = 42	42
Blood glucose sampling (run-in)	0.6	17 samples x 2 periods = 34	20.4
Blood glucose sampling (MMTT)	0.6	24 samples x 2 periods = 48	28.8
Immunogenicity	5	3	15
Total			177.2
Total for clinical purposes [rounded up to nearest 10 mL]			180

Abbreviation: MMTT = mixed meal tolerance test.

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

Protocol I8B-MC-ITSA Sampling Summary for Part B

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20	1	20
Clinical laboratory tests[a]	9	1	9
Pharmacokinetics – insulin lispro	1	21 samples x 2 periods	42
Blood discard for cannula patency	1	21 samples x 2 periods	42
Blood glucose sampling (run-in)	0.6	17 samples x 2 periods = 34	20.4
Blood glucose sampling (MMTT)	0.6	24 samples x 2 periods = 48	28.8
Immunogenicity	5	3	15
Total			177.2
Total for clinical purposes [rounded up to nearest 10 mL]			180

Abbreviation: MMTT = mixed meal tolerance test.

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

Appendix 6. Protocol Amendment I8B-MC-ITSA(d) Summary
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Compared to Humalog in Children, Adolescents, and Adults with Type 1 Diabetes Mellitus

Overview

Protocol I8B-MC-ITSA(c), A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Compared to Humalog in Children, Adolescents, and Adults with Type 1 Diabetes Mellitus, has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Since CCI [redacted] is being provided as an option for the MMTT, clarification was added to allow for only this chocolate drink during the MMTT.

Revised Protocol Sections

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

6.3.2. Caffeine, Alcohol, and Tobacco

Patients should refrain from caffeine-containing food/beverages (e.g., 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 study site visit, excluding the test meal when CCI [redacted] may be given.

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